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MENINGOENCEPHALITIS IN LYMPHOGRANULOMA VENEREUM*

A Report of Two Cases

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LYMPHOGRANULOMA VENEREUM has been extensively studied since 1913, when interest in the disease received added impetus from the report of Durand, Nicolas and Favre.[1] In more recent years evidence has accumulated tending to emphasize the concept that this virus infection is not a localized disease but is in reality a systemic infection.[2-6] Besides the more frequent involvement of the genitals and regional lymph nodes, with or without rectal stricture as a sequela, Van Rooyen[2] has listed the following ways in which lymphogranuloma venereum may manifest itself: involvement of the throat, with inflammation of the tonsils, ulceration or angina; fever, with headache and other pyrexial disturbances; skin rashes; various forms of articular involvement; generalized involvement of the lymph nodes, with splenomegaly and hepatomegaly; granulomatous conjunctivitis; epididymitis; and meningoencephalitis. Harrop et al.[4,5] have extended the clinical knowledge of this virus disease by a description of 3 cases occurring in laboratory workers. In these patients the infection was acute with a septic type of fever, chills and sweats, articular rheumatism, headache and, in 2 cases, cervical lymphadenitis. In the last-named cases, the authors were of the opinion that the patients were infected via the upper respiratory tract, and noted that lymphogranuloma venereum can occur as an acute infection without apparent localization and tissue reaction at the point of invasion.

Of increasing interest has been the demonstration of involvement of the central nervous system by lymphogranuloma venereum. Findlay[7] demonstrated changes characteristic of meningoencephalitis in monkeys, mice, guinea pigs, rabbits and dogs following intracerebral inoculation with the virus. Although the occurrence of severe headaches in human cases was long known, its importance was not sufficiently stressed until von Haam and D'Aunoy[8] published their studies in 1936. They isolated the virus from the spinal fluid of 2 patients during the acute stage of infection, thereby incriminating the agent when the cerebral manifestations consisted mainly of headache. During the same year, Rajam[8] reported a clinically diagnosed case of lymphogranuloma venereum in which there had been surgical interference with the inguinal buboes. This was followed by an acute exacerbation of the illness, with manifestations of severe meningoencephalitis and death. Sabin and Aring[6] recently published evidence that more definitely established this agent as a cause of severe meningoencephalitis in man. On two occasions they isolated the virus from the spinal fluid of a patient showing marked cerebral changes. The virus was also obtained from an inguinal lymph node six weeks after the onset of the acute phase of illness and from a penile wart. Further proof of the etiologic relation of the virus to the illness encountered was found in complement-fixation studies.

In the present paper additional evidence is submitted that lymphogranuloma venereum may be a cause of acute meningoencephalitis. The first case described offers several other clinical features of interest. These include the isolation of the virus from an inguinal lymph node some five months after the onset of illness, the spinal block encountered, the striking spinal-fluid findings and the results of Frei tests and complement-fixation tests with a variety of antigens. In addition, the isolation of the virus and the experiments leading to its identification are detailed.

A second case of meningoencephalitis probably due to lymphogranuloma venereum is briefly described.

CASE REPORTS

CASE 1. L. B. A., a 24-year-old Negro private, was admitted to the Station Hospital at Indiantown Gap, Pennsylvania, on October 24, 1942, in a delirious condition. The date of onset of illness was indefinite. When sufficiently recovered to be questioned, however, the patient stated that he had been in excellent health until the latter part of September, when he first noted the formation of a "knot" about the size of an almond in the right inguinal region. This was followed in a few days by the appearance of a grayish, watery urethral discharge without associated burning or irritation. The

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patient's last exposure to venereal disease had occurred 4 weeks prior to the appearance of the discharge, with previous exposures at 2-week intervals to the same person.

At that time the patient was transferred from Camp Gordon, Georgia, to Indiantown Gap and, while en route, experienced chilly sensations, weakness and severe bifrontal and occipital headache. After arriving at his new post, he went to the Dispensary regularly because of the severe headache. Since his temperature was found to be mildly elevated, he was given analgesics, with little relief. On his calling attention to the urethral discharge, he was given sulfonamide tablets, of which he took 6 daily for one week. This lessened the amount of urethral discharge but did not stop it.

On October 10, still troubled with weakness, chills, feverishness and severe headaches, the patient went A.W.O.L. to visit his home in Texas. There he continued to be ill and was advised by a physician to return to camp. While on the train back to camp on October 24, he vomited twice and was extremely drowsy. He fell asleep, and there followed a period of amnesia lasting for 5 days. He was taken to the Marine Hospital in Pittsburgh and transferred to the Station Hospital at Indiantown Gap on the same day.

Physical examination at that time showed a temperature of 101°F., a pulse of 70 and respirations of 20. The patient was disoriented and confused, and complained of headache and stiffness of the neck. The pupils were equal, reacted to light and were in accommodation. Extraocular movements appeared normal, as were the eyegrounds. There was marked nuchal rigidity. The other positive findings included lower abdominal tenderness, an enlarged and tender right inguinal lymph node, a urethral discharge and positive Kernig and Brudzinski signs. All the reflexes were active and equal, and there were no motor or sensory changes.

The red-cell count was 4,850,000, and the hemoglobin 90 per cent. The white-cell count was 18,400, with 72 per cent neutrophils, 26 per cent lymphocytes and 2 per cent monocytes. The urine was normal. Smears of the urethral discharge revealed many pus cells but no gram-negative intracellular diplococci. A blood Kahn test made on October 29 was doubtful but negative on the following day. A blood culture was negative after 7 days.

Spinal-fluid examination on October 26 revealed the initial pressure to be equivalent to 380 mm. of water (Table 1). Abdominal compression caused a prompt rise in pressure, but there was no increase with jugular compression. The fluid was slightly cloudy, with 612 red cells and 11 white cells per cubic millimeter. The globulin reaction was ++++. Smears of the fluid, as well as those of all subsequent fluids, were negative for organisms, and cultures showed no growth. Roentgenologic examination of the chest and skull failed to reveal any significant pathologic change.

The temperature gradually returned to normal over a period of 7 days, the pulse rate increasing as the temperature declined. The patient's confusion became much less and he appeared less toxic. The signs of meningeal irritation, however, persisted as severely as before. A second lumbar puncture on October 28 showed that the pressure was elevated and again gave signs of block. The fluid was xanthochromic. There were 541 white cells per cubic millimeter, with 20 per cent polymorphonuclear leukocytes and 80 per cent lymphocytes. The globulin reaction was markedly positive.

Mental clearing continued, with a gradual improvement of the memory. The patient had no recollection of events for 5 days beginning on October 24. He complained of blurring of vision and diplopia and persistent headache. By November 6, the stiffness of the neck had decreased and a lumbar puncture again gave signs of block. Marked weakness and pains in the extremities were prominent complaints. Although there was slow, steady general improvement, the patient was transferred on December 12 to the Walter Reed General Hospital in Washington, D. C., because of the persisting spinal block.

At that time the patient did not appear very ill, was well oriented and displayed no mental aberrations. He complained of generalized weakness and headaches. Examination revealed weakness of all four extremities, more marked in the proximal musculature. He was unable to lift his arms and thighs off the bed, but had a fair grip in the hands and fairly strong movement of the toes and feet. The musculature of the extremities was flabby, but fibrillations were not present. The deep tendon reflexes were uniformly hypoactive, whereas abdominal reflexes were absent. To all forms of sensation there was a glove-and-stocking type of hypesthesia, extending to the level of the wrists and to the junction of the middle and lower thirds of the legs.

TABLE 1. *Spinal-Fluid Findings in Case* 1.

DATE	PRESSURE: INITIAL	PRESSURE: AFTER ABDOMINAL COMPRESS.	PRESSURE: AFTER BILAT. JUG. COMPRESS.	PRESSURE: AFTER CUFF COMPRESS. OF NECK	AMOUNT REMOVED	FINAL PRESSURE	COLOR	CELL COUNT	GLOBULIN REACTION	TOTAL PROTEIN	COLLOIDAL GOLD CURVE
	mm. H2O	*mm. H2O*	*mm. H2O*	*mm. H2O*	*cc.*	*mm. H2O*		*cu.mm.*		*mg./100*	
Oct. 26	380	460	380	....	10	....	Cloudy	9L,2P, 612 RBC	++++	....	....
Oct. 28	230	Prompt rise	230	....	10	100	Sl. xantho.	541 WBC (80%L)	++++	....	....
Nov. 6	100	120	100	....	10	....	Xantho.	3L	++++	....	....
Nov. 13	350	....	350	....	10	130	Xantho.	0	++++	....	....
Dec. 1	....	....	....	....	....	....	....	....	++++	3570	5555555555
Dec. 13	110	....	110	110	....	....	Xantho.	8L	++++	2590	5555555555
Jan. 11	130	....	130	130	....	....	Xantho.	10L	++++	....	5555555555,5555432000
Feb. 11	165	275	165	165	15	0	Sl. xantho.	0	++++	438	5555555555,4311000000
Mar. 11	170	300	170	170	20	0	Sl. xantho.	8L	++++	237	5555555433
Apr. 22	215	300	215	215	20	75	Colorless	1L	++++	153	5555555543
May 31	185	250	185	185	15	120	Colorless	5L	+++	114	5555554431

A lumbar puncture on December 13 showed no change in the fluid dynamics. Neck compression by means of a cuff at 40 mm. of mercury elicited no response. The fluid contained 8 lymphocytes per cubic millimeter and a total protein of 2590 mg. per 100 cc., and the colloidal-gold curve was 5555555555. Wassermann tests, as well as Kline diagnostic and inclusion tests and Kolmer complement-fixation tests, on this and all subsequent spinal fluids were negative.

Slow but steady improvement followed, although therapy was nonspecific. Late in December, lymphogranuloma venereum was first suspected as the causative agent. A Frei test was done, using antigen of chick-embryo origin, but was negative. This was repeated on January 10, 1943, and was again negative. The spinal fluid was examined on the following day, with essentially no change from the preceding findings. At that time the colloidal-gold curve in a 20-tube test was 5555555555,5555432000. Mice were inoculated intracerebrally and intraperitoneally with portions of this spinal fluid, but no virus was isolated. Complement-fixation tests on serum obtained on January 15 were strongly positive for the lymphogranuloma-psittacosis group (Table 2). Further Frei tests were carried out, using both chick-embryo and human antigens, the former yielding a questionably positive result, whereas the latter was negative (Table 3).

By that time the patient had improved sufficiently to be able to walk around, but still complained almost daily of bifrontal and occipital headache. There was also pain in the cervical region and upper dorsal spine. This pain was made worse by sudden acute flexion or extension of the head.

On February 22, the single enlarged right inguinal lymph node was surgically removed and half of it sent to the Virus Laboratory of the Army Medical School. From it a virus was isolated and identified as that of lymphogranuloma

venereum. Therefore, beginning on March 3 and continuing through March 26, the patient was given 5 gm. of sulfathiazole daily. A few days prior to the institution of this therapy, the urethral discharge had spontaneously ceased. A further attempt was made to isolate virus from the spinal fluid drawn on March 11, but it was unsuccessful. It should, however, be noted that the sulfathiazole level of this specimen was 0.85 mg. per 100 cc.

TABLE 2. *Serum Dilutions Resulting in Positive Complement-Fixation Tests with Various Antigens.*

Source of Serum	Time After Onset	L. A. Antigen	Lygranum C. F.	Psittacosis Antigen
	mo.			
Case 1:				
November 9, 1942	1¼	1:128	1:64	1:256
January 15, 1943	3½	1:256	1:64	1:512
April 16	6½	1:128	1:32	1:256
May 24	7¾	1:64	1:16	<1:6
May 28	7¾	....	1:16	<1:12
June 4	8	1:96	<1:8	.....
Case 2:	1	1:32	1:64	1:144
Known case of psittacosis	....	1:16	1:32	1:32
Normal subject	....	0	0	0

By April 9, the patient was feeling much stronger, with only mild weakness of the extremities, and the sensory deficits had disappeared. Headache was still present but was not so severe as previously. His course at this hospital was completely afebrile. Improvement continued so that by June the patient was well enough to be discharged home on sick leave. At that time, the spinal block was still present. In addition, Frei tests with Lygranum S.T. and other yolk-sac antigens were positive.

During the hospital stay, extensive laboratory studies were performed. The spinal-fluid findings, complement-fixation determinations and the results of Frei tests are summarized in Tables 1, 2 and 3. Other findings were as follows:

Sixteen complete blood examinations were made, with a normal range of hemoglobin and red cells in all. The initial white-cell count on October 26, 1942, was 18,400, with 72 per cent neutrophils and 26 per cent lymphocytes. Subsequent counts ranged from 5800 to 11,500, with an essentially normal differential except for a mild degree of eosinophilia (3 to 9 per cent). On February 21, 1943, the clotting time was 4 minutes, and the bleeding time 2 minutes. The sedimentation rates in three determinations made over a 4-month period were 20, 20 and 17 mm. per hour. A blood culture taken during the acute febrile phase of the illness showed no growth after 7 days. A doubtful Kahn test was obtained from the serum of October 28, but all subsequent tests were negative. Complement-fixation tests for lymphocytic choriomeningitis, Western equine encephalitis, Eastern equine encephalitis and St. Louis encephalitis were negative.

An intradermal tuberculin test made on May 27, 1943, with 0.00002 mg. PPD (purified protein derivative) was negative, but one made with 0.005 mg. PPD on June 4 was positive.

Blood-chemistry studies made on December 15, 1942, showed the sugar level to be 114 mg. per 100 cc., and the urea level 9 mg. On December 8, the total protein determination was 7.84 gm. per 100 cc. with 4.57 gm. of albumin and 3.27 gm. of globulin per 100 cc. On April 8, 1943, the total protein was 9.0 gm., with 4.82 gm. of albumin and 4.18 gm. of globulin.

Fifteen urine examinations were essentially negative. Urethral smears were repeatedly examined for gram-negative intracellular diplococci, but all were negative. Three urethral cultures for gonococci were negative.

Routine x-ray examinations of the skull, chest and cervical spine were negative, as were special roentgenologic studies of the cervical and dorsal spine and the skull.

Electroencephalographic studies on December 24 showed a slightly slow record, with almost continuous 8-per-second activity in all leads. The dominant rhythm was from 9 to 9.5 per second on March 8 and about 10 per second on March 30. In each test there was a marked build-up with overventilation, with a slow return to the resting state.

The final clinical diagnosis was myelomeningoencephalitis with adhesive arachnoiditis secondary to lymphogranuloma venereum.

CASE 2. L. B., a 22-year-old Negro private, was admitted to the Station Hospital at Fort Bragg, North Carolina, on July 30, 1941. He gave a history of having had coitus without prophylaxis on July 7. Swelling and tenderness appeared in the right inguinal region on July 15 and progressed to the time of admission.

Physical examination was negative except for the painful and tender right inguinal adenitis. The urine was normal.

On August 7, the red-cell count was 4,930,000, and the white-cell count 14,600. A lumbar puncture on August 7 revealed the spinal fluid to be under slightly increased pressure. There were 483 white cells per cubic millimeter, with 75 per cent lymphocytes and 25 per cent polymorphonuclear leukocytes. Smears showed no organisms, and cultures were negative. On August 11, a Frei test was positive.

TABLE 3. *Frei Tests in Case 1 with Various Antigens.*

Date of Test	Time After Onset	Human Antigen	Lygranum S. T.	A. M. S. Antigen	L. A. Antigen	Psittacosis Antigen
	mo.					
December 26	3	....	—	....	....	....
January 10	3½	....	—	....	....	....
January 30	4	....	....	±	....	....
February 5	4¼	—	....	....	....	....
May 25	7¾	....	+	....	+	....
June 1	8	....	....	+	....	—

On August 4, the patient developed frontal and occipital headache and photophobia. This persisted for the next 3 days and then subsided. The temperature during that time was between 100 and 101°F.

A clinical diagnosis of meningoencephalitis secondary to lymphogranuloma venereum was made.

Serum taken from the patient on August 16 and stored at −20°C. was tested 21 months later and gave a positive complement-fixation reaction for lymphogranuloma venereum in dilutions up to 1:64 (Table 2).

VIRUS STUDIES

Although in Case 1 an association between the findings in the central nervous system and lymphogranuloma venereum was suggested by the positive complement-fixation tests, it was thought that isolation of the virus would offer more conclusive evidence of such a relation. Accordingly, efforts were made to isolate virus, even though a considerable interval had elapsed after the acute febrile phase of the illness. These studies are described below.

Cerebrospinal fluid. Bacteriologically sterile specimens of spinal fluid were obtained on January 11 and March 11, 1943, for attempts at isolation of virus. Mice were inoculated intracerebrally and intraperitoneally with 0.03 cc. and 0.1 cc. of the fluid, respectively. None of these animals showed clinical evidence of disease. Several passages were

made in an effort to bring out possible unapparent infection, but without success. All the mice not sacrificed for passage were tested intracerebrally for immunity to lymphogranuloma venereum virus, and were found to be nonimmune.

Lymph node. The right inguinal lymph node noted in the clinical record was removed on February 22, about five months after it had appeared. Grossly, it measured 15 by 10 by 7 mm. and was grayish-white, with a slightly nodular surface. It was sectioned with ease, revealing a 3-mm. rim of lymphoid tissue supported on fatty tissue. Half the node was reserved for virus study and the remainder was fixed for pathological study. Sections of this material were studied at the Army Medical Museum, where the following description was made:

> The lymph node is the seat of low-grade chronic inflammation of nonspecific character as judged by the histopathologic appearances. The capsule is thickened and infiltrated by lymphocytes and plasmocytes, and the trabecular and hilar connective tissue is increased in amount. The follicles are hypertrophied and there is considerable mitotic activity in the germinal centers. The lymphoid and reticuloendothelial elements of the node are hyperplastic, and the latter are actively phagocytic, containing nuclear débris and occasional brown pigment resembling melanin. There is no suggestion of the tuberculoid lesions of lymphopathia venereum. Diagnosis: chronic hyperplastic lymphadenitis, nonspecific.

At the Virus Laboratory, smears were made from the cut surface of the lymph node and stained by the Macchiavello technic. Several minute red bodies resembling the elementary bodies of lymphogranuloma venereum were observed. Blood agar cultures of this material were negative. A portion of the node was ground, suspended in saline solution and injected intracerebrally and intraperitoneally (0.03 cc. and 0.2 cc. of a 10 per cent suspension, respectively) into 6 mice. One mouse appeared ill on the fourth day and was sacrificed. A 10 per cent suspension of the brain was injected intracerebrally into other mice. Cultures of the inoculum were negative. Three more of the original 6 mice showed signs of illness from which they slowly recovered, but the 2 remaining mice failed to become ill.

All the second-passage mice showed evidence of disease four to six days following inoculation. Macchiavello-stained touch smears of the meninges revealed elementary bodies of the lymphogranuloma venereum type, whereas bacteriologic cultures were negative. The virus* was maintained by intracerebral passage in mice.

Characteristics of the Virus

Mice. The L. A. virus was carried through thirteen successive mouse passages before being stored at −70°C. In these animals, following intracerebral inoculation the disease was characterized by roughening of the fur, hunching and weight loss. Frequently, the first sign of illness was that of hyperactivity induced by tactile stimuli, often ending in a tetanic convulsive seizure, with or without death ensuing at that time. Not infrequently, mice passed through this phase of hyper-reactivity into a longer period of apathy, with hunched backs, roughened coats and emaciation. In two or three weeks gradual improvement followed, with apparent clinical recovery. Such mice were usually immune to subsequent reinoculation with the virus.

Brain material from the fourth mouse passage was titrated intracerebrally in mice. Half the mice died in each tenfold dilution through 1:10,000. The remaining mice became sick through dilutions of 1:1,000,000 and then slowly recovered.

Intraperitoneal inoculation with 0.1 to 0.2 cc. of a 10 per cent suspension of fresh infected mouse-brain material did not give rise to clinical disease. Three or four such injections at intervals of a few days to a week usually resulted in immunity to intracerebral inoculation with the homologous strain.

Guinea pigs. Two adult male guinea pigs were inoculated with a 10 per cent suspension of infectious brain material from the third mouse passage, each receiving 0.1 cc. intradermally and 1.0 cc. subcutaneously in the inguinal region. Both animals developed moderate fever — one from the second to the fourth day, the other on the fifth and sixth days. Inguinal adenopathy appeared in one animal, which also developed a vesiculopustular lesion at the site of intracutaneous injection. A red papular lesion was produced in the other animal. Both skin lesions gradually subsided in a few days.

Developing chick embryos. A bacteriologically sterile 10 per cent suspension of infectious brain material from the second mouse passage was inoculated in 0.2-cc. amounts onto the chorioallantois of ten-day developing chick embryos. By the fifth day, central plaque lesions and numerous secondary pocklike foci appeared in about half the eggs. These lesions were usually whitish and opaque, but occasionally clear vesicles were produced. Smears stained by Macchiavello's method showed occasional elementary bodies and plaques. One of the infected membranes was ground into a 10 per cent suspension, and other embryonated eggs were inoculated. Ten-day embryos received 0.2 cc. on the chorioallantois, whereas six-day embryos had 0.5 cc. injected into the yolk sac. About half those inoculated on the chorioallantoic membrane developed lesions. This type of passage was then discontinued.

Of 6 embryos inoculated in the yolk sac, only 1 was heavily infected when examined ten days after injection. This yolk sac was ground, a 1:10 suspension was made, and 0.5 cc. was inoculated into the yolk sac of additional six-day embryos. The L. A. virus was carried through thirteen successive yolk-sac passages before being stored at −70°C. During this series of passages, the best yield of elementary bodies resulted when seven-day or eight-day embryos were inoculated with 0.5 cc. of a 1:50 dilution

*The virus isolated from Case 1 is referred to throughout as the "L. A. virus."

of infected yolk-sac material. Such embryos usually died four to six days after inoculation.

Studies to Establish the Identity of the Virus

The manifestations of infection with L. A. virus in the mice, guinea pigs and developing chick embryos were consistent with those described by others [2,7,9–11] for lymphogranuloma venereum. In addition, parallel infection experiments with a known strain of lymphogranuloma venereum virus were carried out in mice (five passages) and chick embryos (thirteen yolk-sac passages), with essentially identical findings.

The pathologic changes induced in mice intracerebrally inoculated with the L. A. virus were also comparable with those known to occur in these animals when infected with lymphogranuloma venereum.[7] Polymorphonuclear and round-cell infiltration of the meninges was the most striking feature. Although perivascular cuffing of moderate degree was observed, the involvement of the brain substance was minimal.

Further information concerning the identity of the L. A. virus was obtained from cross-immunity tests in mice. The animals were immunized to the virus by repeated intraperitoneal injections* of infectious mouse-brain suspensions. Inoculations were made at intervals of a few days to a week or more, a total of four or five injections of 0.1-cc. amounts being made before a final intracerebral inoculation was made with the homologous virus. Similarly, mice were immunized to a known strain of lymphogranuloma venereum virus. The injected mice were then tested intracerebrally with 0.03 of a fresh 10 or 20 per cent suspension of infectious mouse-brain material of the heterologous strain. Control mice were inoculated in each case. The animals were observed daily. The findings, which are presented in Table 4, strongly indicate similarity of identity of the L. A. and the known lymphogranuloma venereum strains of virus.

TABLE 4. *Cross-Immunity Tests in Mice.*

Experiment No.	Immunizing Virus	Testing Virus	Results of Tests*	
			Immunized mice	Normal mice
1	L. A.	A. M. S.	0,0,0,0,0,0,0,8†	3,7,8,11,S,S
	A. M. S.	L. A.	0,0,0,0,0,0,0,0	2,2,4,4,4,5
2	A. M. S.	L. A.	0,0,0,0,0,0	3,4,S,S,S

*The numeral indicates the day of death of the mouse following the test inoculation; S indicates that the animal showed definite signs of illness but survived at least ten days; 0 means that the animal remained well throughout.

†This mouse probably died of intercurrent infection.

Complement-fixation studies were utilized not only to determine the presence of specific complement-fixing antibodies in the patient's serum, but also as an ancillary aid in identifying the virus isolated from him. The findings are summarized in Table 2, from which it can be seen that these tests were carried out with three different antigens, namely, Lygranum C. F., psittacosis antigen and an antigen made from the virus isolated from the patient and hence labeled "L. A. antigen." Lygranum C. F. is a commercial preparation (Squibb) from yolk-sac material infected with lymphogranuloma venereum virus. It has been used extensively in complement-fixation tests for this disease.[6, 13, 14] The other two antigens were also prepared from infected yolk-sac material using an ether-extraction method. This technic has been applied to the lymphogranuloma-psittacosis group of viruses by several workers.[15–17] Only those yolk sacs that appeared rich in elementary bodies were used in the preparation of the L. A. antigen. Before inactivation of the material, it was titrated intracerebrally in mice. It was found to make all the mice definitely ill in ten-fold dilutions through 1:100,000; however, deaths were few and were distributed unevenly in the various dilutions.

Frei Tests

The above laboratory data indicated that the patient had had active lymphogranuloma venereum infection for at least six months. During that period, however, four Frei tests had been made, with only one questionably positive result (Table 3). A new series of Frei tests was therefore carried out, using antigens of chick-embryo origin.[12, 18] These antigens included the commercial product (Lygranum S. T.); the Frei antigen of the Army Medical School and the L. A. antigen, made from the patient's virus. In addition, it was of some interest to use properly diluted psittacosis antigen in skin tests on the patient, since serologic studies had brought out the usual cross reaction noted for this group of viruses.[19] The last two antigens were diluted in the following manner: yolk sacs were calculated to weigh 1.5 gm. each, and the dilutions were made up to 1:25, 1:50 and 1:75 — that is, 1 part of infected yolk sac was suspended in 25 parts of buffered-saline solution and so forth. Similar dilutions of normal yolk-sac suspensions were used as controls. For testing, the usual 0.1-cc. intradermal injection of each dilution was made, and daily measurements of the lesions were made for seven days. As can be seen in Table 3, Lygranum S. T., the L. A. antigen and the Army Medical School antigen gave positive results, whereas the psittacosis antigen was negative.

Discussion

The diagnosis of these cases as lymphogranuloma venereum was based on the clinical history and physical findings, the positive complement-fixation tests, the positive Frei tests and, in Case 1, the isolation of the virus from the patient. The etiologic relation of the virus to the meningoencephalitic changes is, of course, based on circumstantial evidence — that is, the involvement of the central nervous system along with the virus infection, the knowledge that this virus can produce meningoencephalitic signs in experimental animals, the fact that the virus has been isolated from the spinal fluid of

*Sabin and Aring[6] reported inability to immunize mice by intraperitoneal inoculation with strains of virus isolated from their patient, as well as with known lymphogranuloma venereum virus.

other patients with the disease [3, 6] and the negative serologic results in tests against other encephalitis-producing virus agents. Final proof that lymphogranuloma venereum can cause meningoencephalitis in man must await isolation of the virus from the brain substance in a fatal case and the demonstration of histopathologic changes in the brain tissue consistent with those produced by the virus in experimental animals.

On the basis of the spinal-fluid dynamics (Table 1), Case 1 presented a complete spinal block throughout the eight months he was observed. It is believed that the meningeal involvement early in the course of his illness resulted in subarachnoid block. This syndrome is known to occur in patients with acute purulent meningitis, tuberculous meningitis, yeast meningitis and syphilitic meningitis.[20] Since these causes seem to have been excluded by means of cultural and serologic studies, it appears probable that the adhesive arachnoiditis encountered in this case was a residuum of the lymphogranuloma venereum infection.

In addition, certain other features of the spinal-fluid findings are of interest. The total protein content reached 3570 mg. per 100 cc., gradually diminishing in amount as the patient improved. None of the specimens clotted after standing. The question arises whether the great increase in protein content was the result of the subarachnoid block per se, of the meningeal involvement or of both these factors. Such high levels of protein are encountered extremely rarely, even in the presence of cord tumor.[20] In this patient, the amount of protein gradually declined from 3570 to 114 mg. per 100 cc. It does not appear that this decline was due to the progressive removal of protein by repeated lumbar punctures, since the intervals between them were about the same both when the protein content was extremely high and when it was relatively low. This suggests that the accumulation of protein occurred at a progressively diminishing rate and was therefore not caused by the block alone. Furthermore, Sabin and Aring[6] found that the amount of protein reached 1400 mg. per 100 cc. in the spinal fluid of a patient who presented no evidence of obstruction. Thus, although in the present case the subarachnoid block undoubtedly was a factor, the more important cause of the great increase of spinal-fluid protein was probably the meningitis, which in turn was probably due to lymphogranuloma venereum.

It is of additional interest to note the character of the colloidal-gold curves, which were uniformly of the paretic or first-zone type. On two occasions, twenty-tube tests were performed in order to obtain end-point readings, and the curves were 5555555555, 5555432000 and 5555555555,4311000000, respectively. Merritt and Fremont-Smith[20] have concluded on the basis of their wide experience that this test has no specific diagnostic import and that precipitation of the colloidal-gold solution is indicative only of an abnormality in the protein content of the fluid. That this was the case in this patient appears to be borne out by the data presented in Table 1.

Infection with the lymphogranuloma venereum virus is known to persist for a long time,[2] so that it is not surprising that the L. A. virus was isolated from a lymph node that had been slightly enlarged for five months. It seems significant, however, that the histopathologic changes observed in this node were nonspecific and not at all suggestive of involvement with this virus.

Isolation and identification of the virus is a too elaborate and slow procedure to be used for routine diagnostic purposes. The complement-fixation test thus becomes an especially valuable adjunct in the early diagnosis of infection with the lymphogranuloma-psittacosis group. Unfortunately, with the antigens now in use it is not possible to differentiate these closely related viruses.[19] This similarity was observed in the complement-fixation results with the serums from these two cases (Table 2) and, as mentioned before, other evidence is necessary in order to establish the diagnosis.

The complement-fixation test was also used as a means of identifying the L. A. virus. An antigen was made from yolk sacs infected with the L. A. virus and was used in tests with serum from both patients and from a known case of psittacosis. Positive reactions were obtained with all the serums.

Negative results with Frei tests are not infrequently observed in lymphogranuloma venereum infections. Only one of eight tests done in the case reported by Sabin and Aring[6] was positive. In Case 1, positive tests were not obtained until the eighth month of illness, and included a positive reaction to an antigen prepared from the virus isolated from the patient. Because of the cross reactions noted in the complement-fixation studies, he was also tested against a psittacosis antigen, with a negative result. So far as could be ascertained, there have been recorded no extensive series of tests on known lymphogranuloma patients with psittacosis antigen, so that the significance of this single observation cannot be evaluated.

Summary

Two cases of meningoencephalitis in patients with lymphogranuloma venereum are presented.

A virus was isolated from an inguinal lymph node of one patient five months after the onset of illness, in spite of the fact that the histopathologic changes in the lymph node were nonspecific.

The virus was identified as lymphogranuloma venereum by its effect in mice, guinea pigs and developing chick embryos, by cross-immunity tests in mice and by complement-fixation studies.

Mice were immunized to this virus and to another strain of lymphogranuloma venereum by intraperitoneal injection.

Subarachnoid block, an extremely high total protein and first-zone colloidal-gold curves were observed in one patient. These findings are discussed.

Positive Frei tests were obtained on one patient with an antigen made from the virus isolated from him, as well as with other yolk-sac antigens. An intradermal test on the same patient with psittacosis antigen was negative.

I am indebted to Captain J. E. Smadel, M.C., A.U.S., for his assistance and guidance through much of the experimental work; to Captain E. Roseman, M.C., A.U.S., for supplying the clinical data on Case 1; to Major C. R. Rein, M.C., A.U.S., for special studies on the spinal fluid of Case 1; to Captain H. L. Hamilton, Sn.C., A.U.S., for carrying out the chick-embryo aspects of the work; and to Lieutenant K. Wertman, Sn.C., A.U.S., for his supervision of the complement-fixation studies.

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CARCINOMA OF THE THYROID GLAND WITH A SOLITARY METASTASIS TO THE SKULL

Report of a Case

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BOSTON

THE characteristically slow growth of the solitary metastasis of carcinoma of the thyroid gland to bones, notably to the skull, has been repeatedly observed. In 1871, Mueller[1] noted the tendency of metastatic lesions of the thyroid gland to appear microscopically benign. Cohnheim[2] was led to regard the primary thyroid lesion as a so-called "benign metastasizing adenoma." He used this paradoxical term in an attempt to explain the long-standing presence of the primary tumor in the thyroid gland and of metastasis to the skull without the usual progressive spread and early death so often seen in other forms of malignancy. More recent studies by Simpson,[3] Dinsmore and Hicken[4] and Graham[5, 6] and the opinions cited by Turner and German[7] after their recent careful review of the literature have led to the conclusion that there is no such entity as a benign metastasizing adenoma. Turner and German believe that this type of thyroid tumor is actually a malignant adenoma. In their experience, painstaking microscopic examination of the entire tumor has, in most cases, shown tumor-cell invasion of the blood vessels, stroma or capsule of the adenoma.

These slowly growing metastatic lesions in the bones, prominent in the skull, vertebras and pelvis, may be solitary or multiple. In some cases the lesion may exhibit arterial pulsation, but this is not always present. Because of the slow growth and the relatively isolated nature of the skeletal metastatic lesion, attempts have been made from time to time to remove both the original tumor and the metastatic lesion surgically. In 1941, Turner and German[7] reported 2 cases in which removal of multiple thyrogenic skull metastases was attempted. The first patient had extensive metastases to the skull but survived the operative removal for three years, ultimately succumbing to progressive metastatic spread. One year after operation, a tender, nodular liver developed, followed by the appearance of further metastases in the skull and in the cervical lymph nodes. The second patient had metastases to the skull, pelvis, coccyx and kidneys at the time of operation and died of uncontrollable hemorrhage following attempted removal of the extensive skull lesions. The hemorrhage occurred during elevation of the bone flap.

Friedman[8] has recently reported 2 cases operated on subsequent to January, 1942, with immediate success in removal of both the primary thyroid tumor and the skull lesion.

In the case reported herein, there was a visible solitary metastasis to the right temporofrontal region of the skull and a previously unnoticed large

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calcified adenoma of the right lobe of the thyroid gland. Both these findings were regarded as favorable and fortified the opinion of members of the Thyroid Service and the Neurosurgical Service in their deliberations on ward rounds. Thorough discussion led to the ultimate decision to attempt

FIGURE 1. *Preoperative X-ray Film of the Skull, Showing the Solitary Metastasis in the Right Frontal Area.*

removal, first, of the primary malignant adenoma of the thyroid and then of the skull lesion, which had been proved by biopsy to be thyrogenic.

CASE REPORT

R. S. C., a 52-year-old, Italian housewife, was first seen in the Tumor Clinic of the Massachusetts Memorial Hospitals on December 6, 1940, at which time she complained of a painless lump on the right upper forehead. Four months previously, the lump had appeared immediately after she struck this part of her head against the corner of a medicine cabinet. It had not changed in size and was not painful or tender. She had, however, noted occasional mild right-sided headaches since the injury, and recently a slight discomfort in the region of the lump itself. She stated that her general health was excellent, and that she had no other complaints.

Examination disclosed a mass in the right lobe of the thyroid gland, which the patient had not known to be present. Consequently, she was admitted to the Surgical Service on December 12, 1940, for study. In the right frontal area there was a moderately firm, nontender mass measuring 2.5 by 1.0 cm. This was thought to lie in a bony defect with some elevation of the outer table of the skull. A nonexpansile arterial pulsation was felt, and there was some increase in tension when the patient coughed. In the right lobe of the thyroid gland could be felt the upper portion of an extremely hard mass suggesting a calcified adenoma, almost completely substernal. The left lobe was normal. Laryngeal examination showed normal motion of both vocal cords. The remainder of the examination and laboratory studies showed no ab-

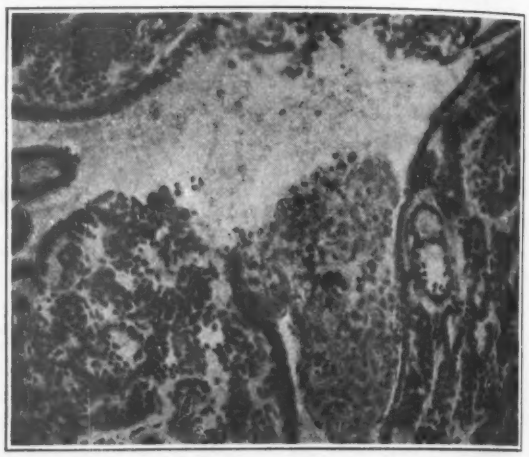

FIGURE 2. *Photomicrograph of a Section of the Thyroid Tumor.*

normalities. A blood Hinton test was negative. Lumbar puncture showed an initial pressure equivalent to 180 mm. of water. The spinal-fluid cell count was 3 lymphocytes per millimeter, with the sugar 79 mg. per 100 cc. and the globulin not increased. The gold-sol curve and Wassermann reaction were negative, and the total protein was 16 mg. per 100 cc. The basal metabolic rate was +11 per cent.

X-ray examination of the skull showed a 3-cm. defect in the right frontal area, involving both tables, with slight surrounding condensation of the bone (Fig. 1). X-ray films of the trachea showed some displacement to the left, with lateral and anterior compression. A calcified mass could be

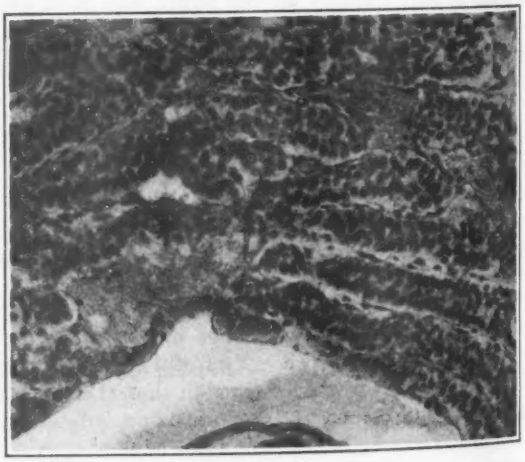

FIGURE 3. *Photomicrograph of a Section of the Skull Tumor.*

seen in the region of the right lobe of the thyroid gland. The chest showed increased fibrosis and no metastases. X-ray films of all the long bones revealed no other lesion. Intravenous pyelograms were negative.

The patient was seen by the neurological consultant, Dr. Theodore J. von Storch, whose impression was that there was no intracranial involvement from the mass other than a questionable slight pressure on the right frontal lobe.

On December 28, Dr. Howard M. Clute performed a right total thyroidectomy and a biopsy of the tumor in the right frontal area. Pathological examination of the tissue was reported by Dr. Charles F. Branch as follows:

The specimen consists of a lobe of thyroid tissue measuring 8.0 by 4.5 by 3.0 cm. and weighing 50 gm., . . . somewhat pear shaped, the smaller end representing the upper pole. . . . The lower three quarters of the gland is represented by a firm, partially calcified, encapsulated, irregularly

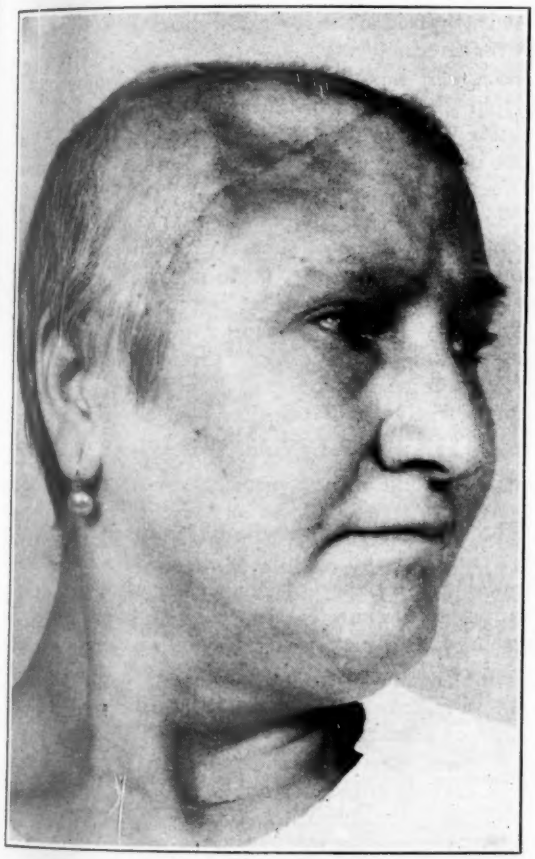

FIGURE 4. *Appearance of the Patient Two Months after Removal of the Skull Metastasis.*
Note the diamond-shaped skull defect, as well as the thyroid scar, three months after removal of the primary tumor.

rounded nodule approximately 4 cm. in diameter. On section, fully two thirds of the central part of this mass is found to be stony hard and calcified. Its periphery, however, is composed of soft, pliable, smooth, glistening, reddish-brown, meaty-appearing tissue in which no normal acinar tissue can be discovered.

Microscopic section through the nodule . . . shows it to consist of closely set cords of small, hyperchromatic epithelial cells having all the appearance of embryonal thyroid tissue (Fig. 2). In certain areas, these cords open up to form well-defined lumens of fetal character containing a small amount of poorly staining colloid substance. . . . There is definite vascular invasion. In spite of their embryonal nature, careful search shows relatively little anaplasia of the epithelial cells, and mitoses are extremely rare.

Section through the biopsy specimen from the skull (Fig. 3) shows a histologic picture practically identical with that above described. . . . Here the cells are slightly more anaplastic, and show a few more mitoses and less evidence of regular alveolar arrangement. Here, also, there is distinct evidence of vascular invasion.

Diagnosis. Thyroid gland: small-cell carcinoma arising from embryonal adenoma and showing vascular invasion. Skull lesion: metastatic carcinoma from thyroid gland, showing local vascular invasion.

The postoperative course was satisfactory, although marked by a rise in temperature to 103°F. on the 2nd day, followed by a gradual fall to normal. Both the thyroidectomy and skull biopsy wounds healed well. Much discussion among the surgical staff and the neurosurgical consultant, Dr. Donald Munro, led to the belief that, in view of the slowly progressive nature of the apparently solitary metastatic tumor, an attempt at radical cure by excision of the skull lesion with subsequent radiation therapy was indicated.

The patient was therefore transferred to the Neurosurgical Service of the Boston City Hospital on January 9, 1941, for further treatment. On January 27, craniotomy was performed by Dr. Munro, and the metastatic tumor was removed. It was found that, although the dura was depressed by the growth, only its outer layer was involved and there was no perforation. Convalescence was satisfactory, and the patient was discharged home on the 10th postoperative day. On this day x-ray therapy was begun, consisting of a series of ten doses of 200 r each, directed at the right temporofrontal area and given over the course of 1 month.

When seen 2 months after the second operation, the patient had no significant complaints. There was a diamond-shaped skull defect measuring 3 by 3 cm. (Fig. 4), with definite pulsation in the area but with no palpable masses. The body weight had remained static.

FIGURE 5. *Appearance of the Patient Two Years After Operation.*

When last seen, 2 years and 6 months after the second operation, the patient was having no difficulty of any sort. She felt entirely well and had gained 6 pounds. There were no palpable masses or evidences of recurrence at either operative site. The defect in the skull had a firm fibrous base, giving sound protection to the underlying brain tissue. The patient's appearance was entirely normal, with normal coverage and distribution of hair (Fig. 5). A check-up x-ray examination of the skull in December, 1942, showed a smooth outline of the skull defect, with no evidence of recurrence or metastatic spread (Fig. 6).

Discussion

The subject of treatment of this disease is a controversial one. In this case, two years of normal health and apparent freedom from metastatic malignant disease seem to have validated the judgment of the physicians involved. Some writers have expressed reluctance to subject a patient to such

Figure 6. *X-ray Film of the Skull Two Years after Operation.*
Note the smooth bony outline of the defect.

radical palliative surgery. Hamann,[9] in reporting a nonoperable case in 1916, expressed the then prevalent opinion as follows:

> As has been pointed out by Bland Sutton and others, metastatic deposits in the skull, manifesting themselves as pulsating, vascular tumors, occur sometimes, secondary to thyroid carcinoma; such metastatic growths are, of course, quite inoperable, as the writer can confirm from an experience in one case in which attempt to remove the growth had to be desisted from, owing to the large size of the blood-vessels.

Cruickshank,[10] however, in 1938 reported the successful removal of a tumor from the right frontal area of a fifty-five-year-old Hindu woman. This tumor was thought to be a meningioma, but pathological examination revealed typical thyroid tissue. Control of hemorrhage had not been troublesome. Four months later a nodule the size of a hazelnut was discovered in the right lobe of the thyroid gland, but the patient refused further operation,—that is, thyroidectomy,—and follow-up studies were not reported.

Barthels[11] has stated that the carcinoma of the thyroid gland that produces bone metastases is of relatively low virulence, and that therefore to remove a single metastatic lesion cannot be described as meddlesome surgery.

Neither the thyroidectomy nor the skull operation proved to be of such formidable nature as to cause severe discomfort or to occasion a prolonged hospital stay. The patient left the hospital seven days after the thyroidectomy and ten days after partial craniectomy, without further disability. Her further course will be studied with interest. Certainly effective palliation has been gained in a situation that had appeared advanced and inoperable.

Summary

The case of a patient who had a carcinoma of the thyroid gland and a single skull metastasis and who showed no evidence of recurrence two and a half years after the surgical removal of both lesions is presented, and pertinent references in the literature are discussed.

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MEDICAL PROGRESS

GYNECOLOGY: CARCINOMA OF THE CERVIX

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CARCINOMA of the cervix is the commonest malignant tumor occurring in the genital tract in women, ranking closely in frequency with cancer of the breast. Its presence may be detected extremely early, for among its symptoms are bleeding and discharge. The tumor can be seen and felt, and is accessible to biopsy. The new vaginal-smear technic,[1] which will be described later, also enables its presence to be detected.

The results of treatment, either radiologic or surgical, are excellent in early cases, yet this disease is found in its early stage in not over 20 per cent of patients seen. The present review of the progress made in all phases of cervical cancer shows that although the results should be markedly improved, they are not. Lack of careful periodic examination of the cervix, appreciation of the significance of abnormal discharges and bleeding and of frequent biopsy of the cervix accounts for many advanced cases. It is also true that patients who have had no symptoms are seen with advanced disease. There is ample evidence, however, that more careful attention to early symptoms and more careful investigation by physicians would result in surgical treatment in the early stages. The results of treatment seem to have reached a level beyond which it is difficult to go. There is no doubt that certain specially treated and studied groups of cases do better than those routinely treated, but on the whole most of the results of the largest cancer clinics show about the same percentages of arrested or cured cases. In other words, it is obvious that more cures will come from earlier diagnosed cases and also from more individualistic treatment.

The theory that all cases should receive combined radium and x-ray treatment, in a routine manner, is not sound. The radiologist should see the tumor and map it out so that he can better aim his x-ray tube at each treatment. The radium available should be of all types and strength. The choice of applicators and needles should be made at the time the treatment is given and not planned before the patient is under an anesthetic, or before x-ray treatment is completed if the latter is given before the radium treatment. Most clinics have radium in certain strengths and in certain types of needles, and this limits the possibility of variation in its use.

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The tendency is to have rules for treatment of the various classes of the disease and to give the treatment always in the same manner. Instead, it should be varied to meet the type and extent of the disease in each case. Every clinic has its set method of treatment, and in each the operators are convinced of the perfection of their method, yet, as already stated, in the end the largest clinics have the same percentage of cures. It is therefore obvious that new methods of attack on the problem must be tried and that treatment should be directed to the cure of the patient, whether or not it consists in the giving of x-ray or radium or in surgery. Taussig's[2] work, to be discussed later, is an example of individualization of cases and the results of his method of treatment are, in his hands, strikingly better than those in most clinics. Miller,[3] of the University of Michigan Hospital, expresses the following viewpoint, which is probably the correct one:

> The limitations of existing methods of treatment are well recognized. No one expects the impossible, but there is good reason to believe that therapy is disappointing. We appear to have reached that comfortable state wherein we hesitate to disturb the efficiency of a therapeutic system which has taken a long time to establish. Perhaps the ease of administration, as well as the apparent effectiveness of irradiation therapy, has lulled us into a state of inertia, in which we fail to exploit existing methods of treatment to their fullest capacity. In radical abdominal hysterectomy, as first performed by W. A. Freund in 1878, and later popularized by Wertheim, was recognized a potent weapon for combating cervix cancer. But, because of its high primary operative mortality rate, and its restricted field of usefulness, the operation was permitted to pass into the discard. Radium and x-ray have also proved their worth. Yet, after almost a quarter century devoted to the refinement of technic and stabilization of procedure, I find there is little to boast about. . . . Perhaps we have reached the end of an era. Perhaps if we could see into the future, we might visualize as the cancer therapist not the radiologist, not the gynecologist nor the surgeon, but possibly the chemist. It is not beyond the realm of possibility that radium may some day become a drug on the market, and deep x-ray therapy equipment an excellent source of copper wire and other spare parts. The limited capacity of existing remedial measures is definitely responsible for some of our restricted success, but any attempt to blame results on this basis alone might more properly be attributed to an indolence on our part — a failure to exploit to their fullest efficiency radium, x-ray and surgery, or a combination thereof — a serious failure to give these methods of treatment a fair chance. . . . In both irradiation therapy and surgery, we have potent weapons. Perhaps neither has been developed to its fullest efficiency. Given an opportunity, these methods may still accomplish what we have a right to expect in the way of vastly improved survival rates.

It is certain that advances will be made in the treatment of this condition. Papanicolaou and

Traut's[4] work on the vaginal smear, Schiller's[5, 6] observations on the staining of the cervix, Hinselmann's[7] use of the colposcope, Taussig's[2] demonstration of the ease and efficacy of lymph-node dissection and our own demonstration[8] of the safety of the radical operation for cervical cancer, when aided by the methods of modern surgery, furnish evidence that more possibilities are open now than ever before.

Etiology

There is no doubt that most cancers of the cervix occur in women who have borne children, but nulliparas make up 5 to 10 per cent of the patients seen in cancer clinics. It is possible that the important factor is not the lacerations themselves but the resultant infections and irritations. Thus, in nulliparas who develop this disease it is conceivable that an endocervicitis or some such lesion as a so-called "congenital erosion" of the cervix has been present. A young girl with menorrhagia recently seen in our clinic had such an erosion. Ten years later the whole area affected was replaced by carcinoma.

> Wharton[9] quotes Pearl as stating: Of 100 American women about 70 are parous and 30 nonparous. In other words, their ratio is as 2⅓ to 1, but the incidence of cervical cancer, on this basis, is as 19 to 1. In other words, with due correction cervical carcinoma is approximately eight times more frequent in parous than in nonparous women. These data indicate that pregnancy or labor does something which predisposes toward cervical cancer.

Severe irritations of the cervix, such as those occurring in patients with procidentia, rarely end in cancer.

Sorba[10] believes that syphilis plays a part in the development of cervical cancer, for 262 patients, or 14 to 15 per cent, of those seen in his clinic had the disease, whereas the percentage of syphilis in other patients was only 1.6 per cent. He thinks that syphilis gives impetus to the cancer. Reports from American clinics do not give such high percentages of syphilis in patients with cancer of the cervix.

Heredity probably plays a role in the etiology of tumors, but a family history of carcinoma is not often present. Imamura[11] found such a history in 9.4 per cent of patients with tumors of the uterus. Wassink,[12] of Holland, in discussing carcinoma of the breast, stated that in many cases there was a family history of carcinoma of the uterus. In our clinics at the present time there are two pairs of sisters with cervical cancer. There is probably a certain amount of truth in the theory of heredity, but in the large majority of cases no family history of cancer is found.

It is interesting to note the infrequency of cervical cancer in Jewish women. Smith[13] found it to be about 5 per cent in the clinic of the Memorial Hospital (New York City), and Healy and Twombley,[14] reporting from the same clinic, stated that only 5 per cent of 920 women patients were Jewesses. This absence of cervical cancer in Jewish women can be explained by breeding out of the disease, since it is apparent that Jews have bred in diabetes and hypertension, or by the Mosaic law in relation to sex, for observance of this law results in the fact that intercourse does not occur during or shortly after the period, when the cervix has just gone through the changes incident to menstruation.

Theories of a hormonic origin have been proposed, and both the pituitary gland and the ovary are considered as possible etiologic factors. Hofbauer[15] believes that the influence of the pituitary gland on the cervix is great, yet this influence must not be direct but through the ovary, which produces estrin and progestin under pituitary influence. Estrin is a growth-producer and is responsible for changes occurring in the cervix. It is well known that Hisaw[16] has been able to produce cancerlike lesions in the cervix with estrin, but the lesions are not real cancers, and are cured by progestin. It is also known that cervical polyps may take on a cellular activity that is similar to cervical cancer during pregnancy. The polyps have a cancerlike appearance when examined microscopically but are not true cancers. The changes are due to some hormonic influence, probably that of estrin. Gardner, Allen, Smith and Strong[17] have been able to produce cancer in the cervices of mice by the use of estrin. These tumors metastasize and can be grafted and grown without more estrin. Other experimenters have produced cancer with estrin in other organs in the animals, but there is no proved case of production of the disease in a human being in this manner. In patients with cancer of the genital tract, however, estrin therapy should be avoided until it has been proved to be safe.

There is no known etiologic factor in cervical cancer, but childbearing, lacerations, infections, syphilis, hormones and heredity all play a part. A tendency to cancer must be present, and some other factor must be the spark that starts the fire.

Symptomatology

No new symptoms have been described to suggest the presence of cancer of the cervix, but meticulous attention must be paid to abnormal bleeding or discharge, whether spontaneous or following douching or intercourse. When continuous bleeding, discharge or pain occurs, the cancer has probably grown beyond the early stage. Miller[18] states that the most significant early symptom is abnormal bleeding.

Diagnosis

There have been added to current diagnostic methods three extremely valuable aids.

Schiller's[6] test is valuable if its indications are interpreted correctly. Schiller used Lahm's discovery that in cancer of the cervix the epithelium lacks glycogen, which is present in normal cervical epithelium. He therefore thouhgt of iodine, which

stains glycogen, as a test for its absence. He advocates a solution made up of 1 part iodine, 2 parts potassium iodide and 300 parts distilled water. In our clinics this solution has not been found satisfactory, since it stains too lightly; the amount of iodine has therefore been increased to 2 parts and that of potassium iodide to 4 parts. This solution is highly satisfactory. Iodine is poured into the vagina, left for two or three minutes and gently reabsorbed with cotton, and the cervix is then viewed.

The most valuable aid that can be obtained from Schiller's solution is indication of the area from which a biopsy specimen should be taken. Any area that stains a homogeneous dark brown can be considered normal, and any area without a stain should be biopsied. Light-brown areas are usually those of diseased or infected epithelium. Superficial cancer does not stain, nor do hyperkeratotic areas due to prolapse, similar areas due to syphilis, or desquamation of the upper layers of the epithelium. Schiller advocates scraping off the abnormal area with the sharp edge of a spoon and fixing and staining, but it is safer to excise the area with tissue on all sides of it. A positive Schiller reaction does not mean that cancer is present, but it does indicate abnormal changes in the cervix, and these should be viewed with the microscope.

The colposcope of Hinselmann is also of great value, not so much for the actual discovery of early cancer as for showing the operator what the cervical epithelium looks like. Once the examiner learns the appearance of the normal cervix, he begins to see abnormal areas and recognizes some of them as due to infection, cysts, exposed ducts and so forth. He also recognizes areas of ulcerated or hypertrophied epithelium divided by fine lines into squares and takes biopsy specimens from them. The use of Schiller's iodine solution in conjunction with the colposcope further demonstrates abnormal cervical epithelium. It has never been my good fortune with either of these tests to find a cancer of the cervix that had not been suspected, yet the amount of information obtained from the study of the cervix by these methods has been enormous and no doubt contributes to one's ability to recognize early, suspicious areas of cervical epithelium. Certainly the constant use of these two methods is of extreme value to the examining physician.

The diagnosis of cancer of the cervix by means of the stained vaginal smear was first introduced by Papanicolaou and Traut.[1] Their work was substantiated by the investigation of Meigs, Graham, Fremont-Smith, Kapnick and Rawson.[19] There is no doubt of the value of this method, and the percentage of correct diagnosis is extremely high. A positive smear usually results in a correct diagnosis, but a negative one means little; the latter is comparable to the negative Wassermann reaction, which does not mean that syphilis is not present. The apparently false-positive smear has yet to be proved. To do this would mean taking out the whole uterus and cutting serial sections along its entire length. The positive smear, in the absence of obvious cancer, may be a means of detecting extremely early growths. This part of the research has not been concluded. It is also possible to differentiate cancer of the endometrium from cancer of the cervix by the smear. A description of the method of taking the smears, the fixing and staining and the interpretation of results is given by the authors mentioned above. This method of diagnosis constitutes an epochal advance, and with Schiller's iodine and the use of the colposcope should aid early diagnosis. Possibly every woman over the age of thirty should have routine vaginal smears done once or twice a year, and be checked by the Schiller test and the colposcope at least once a year. A positive smear means that an investigation should be carried out under anesthesia. The uterus should be dilated and curetted and specimens of the cervix removed for microscopic section.

Biopsy. Study of the cervix by means of biopsy is the most important of the diagnostic aids. The specimen should be taken with supposedly healthy tissue on all sides of it. This is not always possible in the office, but it can always be done under an anesthetic. The disadvantage of the biopsy is that it can be negative and yet cancer can be present in the cervix. To be sure that it is not present, nearly all the cervical tissue would have to be removed. By means of the iodine test and the colposcope the most suspicious area can be demonstrated and biopsied.

Classification

The subject of classification is not necessarily included in a discussion of progress, but unless a single classification is universally agreed on, results and treatment cannot be compared. Comparison of the results in various clinics is at best inaccurate, but with different methods of classification adopted it is rendered even more so.

It is essential that tumors be classified, for certain clinics have a greater preponderance of early cases than do others. Cancer hospitals where patients can remain for treatment usually have larger numbers of advanced cases than do general hospitals. Since the League of Nations classification[20] is being universally accepted as the proper one, it is being favored more and more by American clinics. This classification is more complicated than the earlier one of the American College of Surgeons or the Schmitz[21] method, and is not a great improvement.

The microscopic grading of the actual tumors is based on the individual ideas of the pathologist, and each one teaches his associates and students accordingly. It is doubtful whether there ever will be a standard method of grading tumors, but the

Martzloff[22, 23] method is to be recommended. His cases are grouped as those with spinal cells or low-grade malignancy, those with transitional cells or medium-grade malignancy, those with fat spindle cells or high-grade malignancy and those with adenocarcinoma. If Martzloff's method could be used everywhere, great knowledge would accrue, but that it will ever become universal is unlikely.

Chambers[24] reports that in his attempt to grade 728 cases, 228 could not be classified because of insufficient tissue. Ten per cent were adenocarcinoma. Of the entire series, 15 per cent were Grade I, 9 per cent Grade II, 54 per cent Grade III and 22 per cent Grade IV — with extremely rapid growth. Chambers finds some indication that the more undifferentiated growths are frequent in youth and that there is no relation between the duration of symptoms and the extent of the disease, and states that most growths involving the cervix alone were cured without respect to their grade. Wetterdal[25] finds the percentage of cures of different grades to be so similar that the microscopic appearance of the cancer is of no apparent prognostic value.

Cancer of the cervix in gross may be of the cauliflower type and everting, or ulcerating and inverting. It may involve the entire endocervix without breaking the mucous membrane of the cervix. It may appear early and yet involve the pericervical tissues and even extend laterally to the pelvic walls. It may be early and appear to be localized and yet have metastasized widely. It may produce enormous growth into the vagina and yet have a favorable prognosis, no extension having occurred into the vagina or pelvis.

Microscopically, cancer of the cervix is usually squamous-celled or epidermoid. About 6 per cent of the tumors are adenocarcinomas according to nearly all authors, and the results either with combined radium and x-ray or with surgery are the same as those in the epidermoid types. All tumors of the endocervix are by no means adenocarcinomas; most of them are epidermoid or squamous, the tumor probably arising from areas of embryologic squamous epithelium resting in the endocervix or from areas of metaplasia. Simpson, Thibaudeau and Burke[26] say that the ratio of adenocarcinoma to squamous-cell carcinoma is 1: 26. Incidentally, 20 patients (32 per cent) of their 63 patients with adenocarcinoma were nulliparous.

Treatment

In a paper such as this it is not pertinent to go into the details of treatment used by each clinic. The references will guide anyone interested to the proper papers related to the subject.

Some clinics prefer to use radium alone in the treatment of this disease. The radium is applied in the canal of the cervix, against the cervix, against the sides of the cervix in the vaginal vaults, in square boxes or colpostats, interstitially by means of glass, gold or platinum seeds, or interstitially by means of platinum needles ranging in strength from 1 to 50 mg. The radium in some clinics is in the form of radon; in others, the platinum-encased salt is used. Certain operators prefer a small amount for a large number of hours; others prefer a large amount for a small number of hours. Some space the treatments four days, seven days or two weeks or more apart.

The use of x-ray treatment is much commoner than formerly, and some clinics employ it as an adjunct to radium, giving it when it is thought that the broad-ligament extensions are not being treated satisfactorily, whereas others use it as an integral part of the treatment. In the latter group it is given either before or after radium treatment. Some surgeons give radium first, then x-rays and then radium again. X-ray treatment is adopted either in an attempt to destroy cancer in the pericervical tissues or broad ligaments and lymph nodes, or to cause cicatrization of the lymphatics of the broad ligaments and destroy lymph-node extensions.

There are many combinations of treatment, and without doubt in every clinic at some time every possible combination has been used. It is interesting that out of the wealth of experience no one method of treatment has been so satisfactory that it has been universally adopted. Apparently, any well-applied treatment that gives radiation in lethal doses to the entire tumor and its surrounding tissue is all that is necessary, and this may be accomplished in a great many ways. It is almost universally agreed that x-ray treatment cannot destroy cervical cancer in lymph nodes. Thus, surgical removal is necessary, but in most clinics it is not used. Bonney[27] writes:

> I have on many occasions, at the close of the operation, discovered an infiltrated gland or mass of infiltrated cellular tissue so adherent to the great vessels as to be irremovable. All of the patients were treated by x-ray, but in spite of a definite target to aim at not one was saved.

The use of x-ray treatment to reduce the size of the cervical growth and cicatrize the broad ligaments, and perhaps to destroy cancer in the lymphatics, is proper. There are those who use x-rays to cross-fire the cervix, hoping to aid the radium in its action, and there are others who direct them straight through the pelvis to injure or destroy the growth lateral to the cervix. All methods are helpful, but no single correct one has been evolved. One of the most important functions of the roentgenologist is to direct the rays at the tumor; yet in many institutions the aiming is left to x-ray technicians. This is a weak point of roentgenologic treatment. From observation of patients treated by x-ray in the early days, it is obvious that the treatment was directed much too high, as evidenced by telangiectases.

The addition to the x-ray armament of the 500,000-volt and 1,000,000-volt machines may or may not be a distinct advance. A sufficient number

of cases over a sufficient number of years to allow any positive statement have not been reported. It is the opinion of the surgeons attending the clinic at the Massachusetts General Hospital that we have not yet learned how to use the 1,000,000-volt machine to the best advantage, and that it well may be that through trial and error we shall hit on the proper dosage. It is our opinion that at times this machine performs wonders, but so does the 200,000-volt machine. It is too early to know what voltage is best.

Merritt[28] advocates the use of the vaginal cone in administering x-ray treatment to the cervix. This is done through Ferguson speculums, and a total dosage as high as 6000 r may be given. This method may have value, and further reports of its results will be eagerly awaited. So far, Merritt has treated 112 patients. He believes that his results are better than those attained with many additional portals and with radium alone.

To sum up, x-ray and radium alone or in combination usually destroy cancer involving the cervix, the cervix and vagina, and the cervix, vagina and pericervical tissue, if it is not in the lymph nodes. Yet there are certain radioresistant tumors that they cannot destroy. Furthermore, a satisfactory destructive dose cannot be given in the advanced stages of the disease without also destroying the bladder and rectum and other important organs.

In 1933, Leveuf, Herrenschmidt and Godard[29] advocated the removal of nodes in pelvic cancer, believing that although cancer of the cervix can be cured by x-ray treatment, lymph-node extensions cannot. In 1934, Taussig[30] first reported the results of dissections of the lymph nodes in a group of patients who had node extension as felt by pelvic examination (Stage II, League of Nations classification). His dissection was done before, during or after radiation, depending on when the patient was admitted to the hospital. Taussig believes that combined radium and x-ray treatment will cure the local disease but that surgery must be employed to cure lymph-node extensions.

I had the privilege of seeing the late Dr. Taussig operate and watched his meticulous dissection of the lymph nodes and lymph chains in the region of the common iliac artery, that of the external iliac artery and vein, that of the internal iliac or hypogastric artery and that of the obturator foramen and its nerve. Some of the nodes were not over 1 mm. in diameter, yet cancer was found in them, whereas in some of the larger ones no cancer was found. Taussig at times found it necessary to resect the external iliac vein during his operation. The only area that to an observer was not satisfactorily cared for was that near the ureter, and there it would have been necessary to tie off both uterine arteries to do a proper dissection. Taussig believed that combined radium and x-ray treatment was satisfactory for this area. As reported in his last paper,[31] he operated on 175 patients with a mortality of only 2 per cent. Of 70 patients in Class II of the League of Nations classification, 37 per cent were living and well after five years. In a parallel group of 118 patients treated by radiation alone, the five-year salvage was only 23 per cent. In other words, Taussig demonstrated a 68 per cent greater salvage if lymph-node dissection was added to radiation. In 27 per cent of his cases cancer was present in the lymph nodes; 21 per cent of these patients were well after five years. If their treatment had been left to radiation alone, probably none would have survived.

Because combined radium and x-ray treatment has failed to be more successful, because of the damage that can be done with radium, because of Bonney's and Taussig's success in dealing with the lymph-node problem, and even more because of Lynch's[32] work, which showed viable cancer in the cervix after satisfactory radiation, the question whether the radical or Wertheim–Clark operation should be revived is pertinent. Bonney in England and Lynch and Morton[33] in California advocate radical surgery, and I have now joined them. Bonney has operated on 500 patients with a mortality of over 9 per cent. He has treated advanced cases and has had to resect veins, arteries, the bladder and the bowel, and has attacked any cases that he thought he could possibly handle. It is difficult to compare his results with those following any form of radiation treatment, but they are excellent. It is obvious that before the operation can be universally adopted the mortality must be lowered. Bonney has kept 40 per cent of his patients well for five years, but he could not operate on all cases. Of his 500 patients, 300 had normal lymph nodes and 200 had cancerous nodes. His ability to cure lymph-node extension is the same as Taussig's, about 22 per cent of his patients surviving for five years.

It occurred to me after reading the reports of Bonney and Lynch and seeing Taussig's work that in selected good-risk patients the radical surgical operation could be done with less mortality and perhaps with as good results as those of radiation, and with a chance to cure certain patients with lymph-node extensions. The operation has been carried out in 57 cases; the mortality was zero, but the incidence of injury to the ureter was unexpectedly high — 10 per cent. The lymph nodes were involved in 16 per cent of the cases. The results indicate, however, that a judicious selection of patients for x-ray, radium or surgical treatment is going on that may lead to new heights of curability. The acme of radiation therapy has not been reached, but it can certainly do no harm to operate on patients with radioresistant tumors and those with involved lymph nodes, especially since the mortality can be kept low.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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CASE 30191

DIFFERENTIAL DIAGNOSIS

DR. MERRILL C. SOSMAN†: If you do not object, I should like to reverse the usual order of procedure. Having been invited "downtown," I assume that the x-ray plays an important part in the diagnosis of this case. So I think that it is fair to start with the films alone without knowing anything about the history and see how far we can go by study of them. That is what I did with these films, which were sent to me the day before yesterday — I went over them thoroughly before I saw the history. It is not a completely honest or unbiased opinion because the roentgenologist knows simply from the way the films have been taken what they were thinking about; but perhaps it is as honest as any roentgenologist can be. Now let us look at the x-ray films.

The lungs are clear — no sign of tuberculosis or tumor so far as I can see. With clear lungs like that we can disregard the rales and rhonchi that come up later. The left half of the diaphragm is elevated. That is the only abnormality that I see in the chest film. The heart is normal in size and shape. Nearly all patients suffering from heart failure have an enlarged heart. The two exceptions are angina pectoris, where the heart may be normal in size and shape, and Addison's disease, where the heart is smaller than usual.

The next three roentgenograms are plain films of the abdomen. One was taken face up, the second face down, and the third upright. They all show a mass in the left flank about 15 cm. in length and 12 cm. in width (Fig. 1). It is smoothly outlined with a peculiar pattern of air in its center. Apparently there is large bowel here, close under the left diaphragm, which rules out an enlarged spleen, since the colon is usually below it. Here is a large, irregular collection of air, which we must consider later. The upright film shows several fluid levels, but no evidence of obstruction. There is a mass in the flank, and the first consideration is the left kidney. Starting out with an intravenous pyelogram, according to the dates we have here, both renal pelves are perfectly normal, so the mass is obviously not part of the left kidney. The ureters are also normal, with no evidence of obstruction. The bladder is well filled, also normal.

We have a large mass then, presumably with a necrotic center, in the left flank, and it is not kidney. Furthermore, the retroperitoneal shadows and the kidney shadow itself, as well as the iliopsoas shadow,

*On leave of absence.

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stand out quite well, so presumably it is not a retroperitoneal mass or it would displace the kidney more.

The next x-ray, according to the dates on these films, is a barium enema. I am a little confused concerning the exact sequence of events. You can help me out here, Dr. Robbins?

Dr. Laurence L. Robbins: The next thing actually done was not the barium enema, but a swallow of barium given at night; no films were taken and that explains why you see the collection of barium overlying the distal transverse colon at the time of the barium enema.

Dr. Sosman: That is the thing I could not understand. Here is the barium enema outlining the colon, which looks perfectly normal. The descending colon is here, lateral to the mass, and above the mass in the transverse colon. But in the mass there is some barium, which looks as if it might have come through a communication from the descending colon to the center of this mass, but the explanation Dr. Robbins gave is satisfactory.

The next examination was a gastrointestinal series (Fig. 2), and now we see this large irregular, tube-like collection of barium in the left flank, corresponding exactly to the air-filled shadow we saw a moment ago. That cavity in the mass communicates with the gastrointestinal tract, presumably not with the colon. The stomach is pushed upward over the mass and that leaves the small bowel as the point from which the barium enters the mass. There are numerous spot films; do they show the communication?

Dr. Robbins: No.

Dr. Sosman: Here is one that shows a mixture of fecal material and barium in the mass, as well as the small sausage-shaped outline.

To summarize the x-ray films, we have a large tumor mass in the left flank that communicates with the small bowel and does not arise from the kidney. Presumably it is part of the small bowel itself, judging from the size and shape of this cavity here. There is no obstruction. It is in the left flank and is either part of the small bowel or directly connected with it.

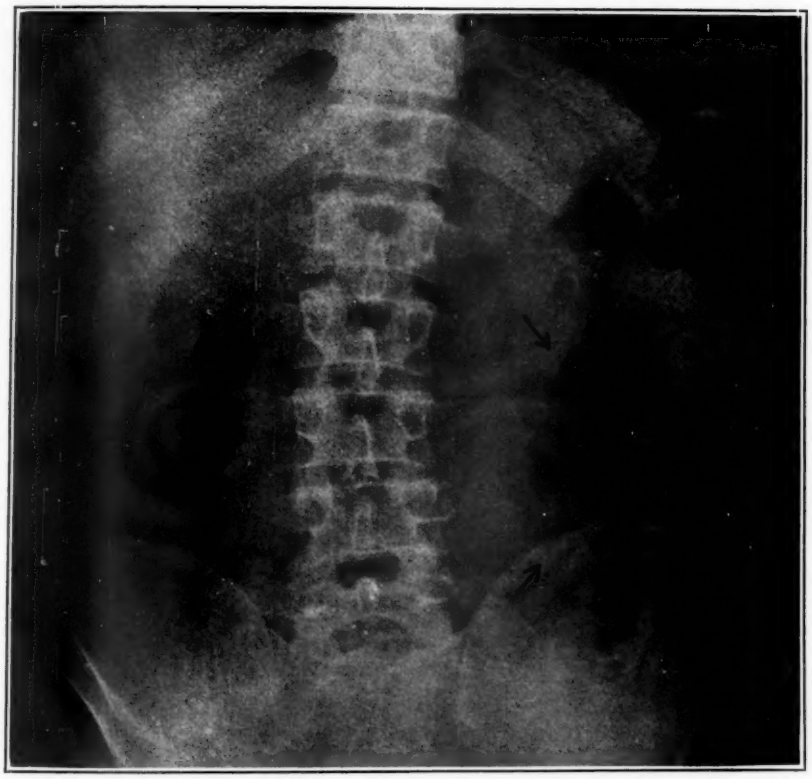

Figure 1. *Plain Film Showing Mass with Air-Filled Necrotic Center.*

Now let us go to the history and see if we can get any leads regarding what type of tumor mass it might be.

Presentation of Case

A thirty-five-year-old elevator operator entered the hospital because of pain in the left upper abdomen.

The history was rather unreliable and more or less contradictory. He was in apparent good health, except for an occasional stomach-ache relieved by soda, until two weeks before admission, when he

was seized by sharp pain in the left upper abdomen, which doubled him up. The pain lasted two or three days. Associated with the onset of his illness, or perhaps later, he developed chills and fever, marked anorexia and nausea. There was no vomiting. He had nocturia (one to three times), dysuria and urgency. He had two painful bowel movements with bloody stools during the week preceding admission. He apparently continued to work until the day of admission, when he had a recurrence of the severe pain in the left upper abdomen. No other information was available except that "he had lost a good bit of weight."

The patient broke his leg when he was seven years old, and at twenty-two he had a penile lesion.

Physical examination showed a well-developed, acutely ill, slightly stuporous man. A transient pleural friction rub was heard over the right apex anteriorly. There were a few fine basal rales on both sides, and occasional rhonchi at the right base. The left portion of the diaphragm was splinted. The heart was normal. There was marked tenderness and spasm in the entire left abdomen, most marked opposite the umbilicus and out toward the flank. Pain and tenderness were also elicited on percussion over the left costovertebral angle. Peristalsis was normal. The patient had pain in his abdomen when he coughed, but there was no rebound tenderness or masses. The prostate was of normal size, but boggy.

The blood pressure was 120 systolic, 75 diastolic. The temperature was 100.8°F., the pulse 76, and the respirations 16.

Examination of the blood showed a red-cell count of 3,500,000, with 65 per cent hemoglobin. The white-cell count was 7400. The specific gravity of the urine was 1.006, with rare red and white cells in the sediment. The stools gave a +++ guaiac test. A blood Hinton test was negative. The blood nonprotein nitrogen was 21.5 mg. per 100 cc., and the protein 4.7 gm.; the chloride was 102 milliequiv. per liter.

A swallow of barium showed a normal esophagus. The stomach displayed a pressure defect and elongation. A small barium enema twenty-four hours later showed ready flow of the material to the cecum without delay. A large amount of gas and fecal matter was present, making the examination unsatisfactory. In the left upper quadrant a long, irregular mass of barium was seen, measuring 15

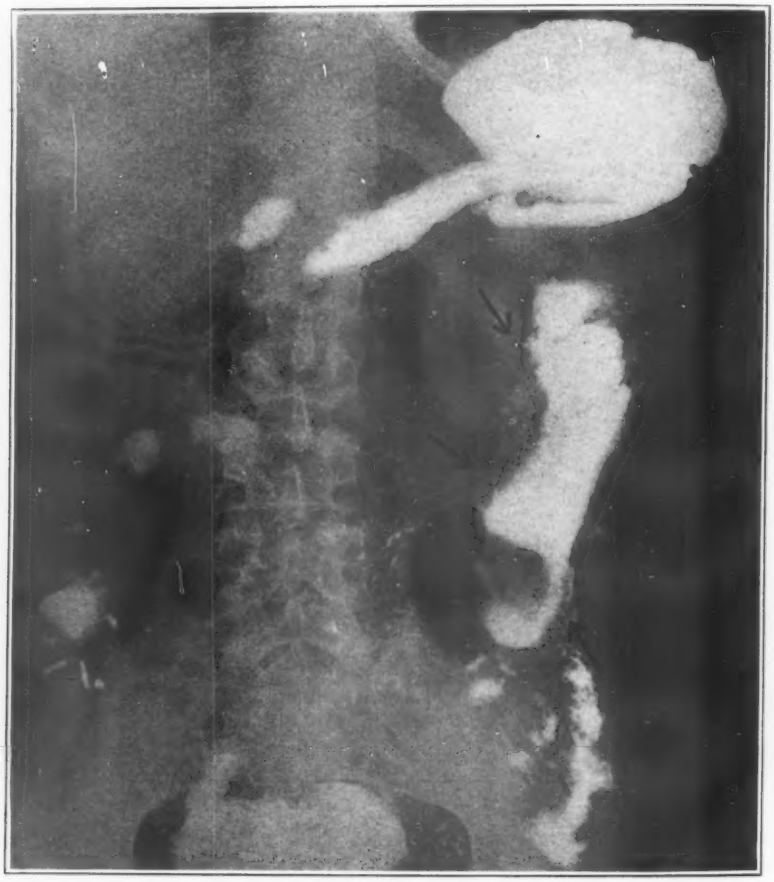

FIGURE 2. *Barium in Air-Filled Necrotic Mass.*

by 6 cm., which lay medial to the upper part of the descending colon and unattached to it. This apparently represented the barium swallowed twenty-four hours earlier. An intravenous pyelogram showed normal kidneys, ureters and bladder. There was a 15-cm. mass in the left midabdomen. Within the mass a large, air-containing, irregular cavity was seen. The fundus of the stomach was displaced to the left. A peculiar defect, thought to be due to an anatomic variation, was noted in the right ninth rib posteriorly. A gastrointestinal series showed a normal esophagus, but in the stomach there was a pressure defect, which seemed to be caused by a mass that lay behind and below it. This mass contained barium and apparently had no intimate connection with the stomach. The duodenum was normal, but the distal part was narrowed and displaced medially by the mass. It was thought that barium entered the tumor from the upper loop of the jejunum, but this was uncertain. The mass did not seem to cause obstruction. An x-ray film of the chest was negative except for increased density in the left lower lobe.

The patient's condition remained essentially the same. The temperature ranged between 100 and 103°F. Daily intravenous fluids and 2.5 gm. of sodium sulfadiazine were given. He had a moderate degree of rectal bleeding, but no vomiting. He was given two transfusions, and on the sixth hospital day an operation was performed.

Differential Diagnosis (*Continued*)

Dr. Sosman: There is a perfectly good possibility in a case like this that the histologic diagnosis could have been made from the stool, if the patient had been observant and had saved the specimen, since he may have passed some tumor. I assume that the chills and fever and the acute episode were due to the necrosis of the center of the tumor and subsequent discharge into the gastrointestinal tract. I do not believe that our medical students are taught to study the stools thoroughly enough. A great deal of information can be obtained from them. Only the pediatricians examine stools with great thoroughness.

The penile lesion brings up the possibility of gumma. A gumma in the gastrointestinal tract is extremely rare. I have seen two or three in the stomach. I do not believe that I have ever seen one in the small bowel or colon that was confirmed. Later on we find that the Hinton test was negative. It is an extremely sensitive test and it certainly should be positive if this were a gumma.

"There were few fine basal rales on both sides, and occasional rhonchi at the right base." These are the rales and the rhonchi that we threw away at the beginning of the exercise. We will leave them there.

Do the statements made in the abdominal examination mean that they did not feel a mass in the left flank? The record seems to imply that tenderness and spasm had obscured the mass. The patient had a moderate anemia (3,500,000) and a normal white-cell count, and the urine was negative. The nonprotein nitrogen was within normal range, and the blood protein was low.

I have already described most of the x-ray findings. The irregular mass containing barium, 15 by 6 cm. in size, which was apparently a false pocket in the tumor mass, I have described. I forgot to mention the small defect in the ninth rib posteriorly, but I think that is a congenital anomaly, sharp and clearly defined.

It is difficult at times to tell exactly where a fistula occurs. Barium runs around through the gastrointestinal tract with a great deal of variation or hesitation. It is sometimes impossible to say where the barium enters any given fistula or abnormal pocket. To sum the whole thing up, I think that this tumor mass in the left flank communicated with the bowel, in all probability with the small bowel. Then we have to try to line up all the various tumors that could occur in a thirty-five-year-old man with a very short history. Abscess, of course, is one of the first things to think of, but he was too young for diverticulitis. The usual diverticulitis of the colon occurs almost entirely beyond the age of fifty and is much commoner after sixty. There is no evidence of diverticulitis in the barium enema. If this man had been a farmer, or a man with similar occupational hazards, he would have been more likely to end up with actinomycosis. He had only a moderate fever, with a normal white-cell count, so that the diagnosis of abscess or inflammatory process is improbable. Tuberculosis is a possibility — a big broken down mass of tuberculous glands. It also would give more fever, and it is in the wrong location; usually it is in the right lower quadrant in the ileocecal region and frequently shows calcification, which I am unable to see in this particular case.

That leaves us, so far as I can think over the possibilities, with only a true neoplasm to consider — a neoplasm in a young man that had apparently developed rather rapidly. At least the patient had lost a good deal of weight, but the record does not say over what period of time. Neoplasm in a man of this age is usually sarcoma, arising in the bowel wall: a leiomyosarcoma, sometimes a lymphosarcoma or spindle-cell sarcoma or occasionally even an angiosarcoma. He passed a moderate amount of blood but had no extensive hemorrhage. We do not have to assume that this was a particularly vascular tumor. The red-cell count was only 3,500,000 — no marked anemia. Some authors have reported cases of melanotic sarcoma in the gastrointestinal tract, but the point of origin has always been doubtful. They are more probably metastatic from cutaneous melanomas. The carcinoids, or argentaffinomas, are rare tumors and are nearly always small and are not apt to ulcerate. I throw them in simply as rare and

unusual possibilities. I should say that this belongs in the sarcoma group, probably originating in the small bowel, with an area of ulceration in the center of the tumor.

DR. BENJAMIN CASTLEMAN: Have you any preference among the sarcomas?

DR. SOSMAN: I have no preference. By taking the broader basis, I have more chance of being right. There is no reason to specify. Obviously it was a surgical problem, and the next thing to have been done was to explore the patient and see what could be done about it. The most we have done is to locate the lesion and to give an idea as to the type of tumor it might have been.

DR. CASTLEMAN: Are there any other suggestions?

DR. CHARLES G. MIXTER: Dr. Sosman ruled out the possibility of chronic or subacute abscess, the result of perforation, simply on the basis of the normal white-cell count and lack of fever.

DR. SOSMAN: That is true. An abscess in a man of this age is extremely rare. About the only reason for one would be perforation by a foreign body, such as a fishbone.

DR. MIXTER: That is what I was thinking about.

DR. SOSMAN: I have seen one in the spleen, — an abscess with a fishbone in the center of the abscess,— but this tumor mass had a thick wall, which I should not expect to see in pyogenic abscess.

May I ask how the X-ray Department interpreted the films?

DR. CASTLEMAN: They thought it was a malignant lymphoma.

DR. HORACE K. SOWLES: We discussed the case with Dr. Robbins the day before operation and came to about the same conclusion as that of Dr. Sosman, suggesting leiomyosarcoma or lymphoma as the most likely diagnosis. At the time of operation there was a large mass, involving the whole left abdomen, with a good deal of surrounding inflammatory reaction; it was bounded superiorly by the transverse colon and laterally by the descending colon and anteriorly was quite adherent to the anterior abdominal wall. In separating the anterior abdominal wall from this mass by finger dissection we went directly into an abscess cavity filled with mucopurulent material, and after a little more finger dissection, we brought up into the wound a loop of small bowel almost completely transected, with wide-open ends of small bowel, and tumor mass. It was possible, however, to isolate an afferent and efferent loop of the small bowel going into this area, to excise the wide-open portion, as well as a segment measuring 12 to 15 cm. on each side of it, and to do an end-to-end anastomosis of normal small bowel at that point. I did not see any particular object in trying to dissect farther, and I was afraid also that we might end up with a wide-open end of colon, which would not be easy to handle. We did the anastomosis, excised the area of small bowel, put a drain in the lateral gutter through a stab wound and closed the incision.

CLINICAL DIAGNOSIS

Malignant lymphoma or leiomyosarcoma of small intestine.

DR. SOSMAN'S DIAGNOSIS

Sarcoma of small intestine.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, lymphoblastic type, of small intestine.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The specimen we received contained a submucosal ulcerating tumor of the small intestine, about 3 or 4 cm. in length. It extended out into the mesentery of the small bowel as a extraluminal tumor mass measuring about 6 by 4 by 2 cm. Thus, a large extrinsic tumor and a smaller intrinsic one were present. On section they presented the uniform pinkish-gray smooth surface of lymphoma. Microscopically it proved to be of the lymphoblastic type, or what some prefer to call "lymphosarcoma."

DR. SOSMAN: Were there any palpable lymph nodes?

DR. CASTLEMAN: No nodes were found in the fat around the small bowel. It has been our experience that, in the majority of cases of malignant lymphoma of the stomach or intestine, the regional nodes are not involved.

DR. SOSMAN: That is the point I wanted to bring out: a solitary lesion in the gastrointestinal tract is susceptible of cure.

DR. CASTLEMAN: In cases of carcinoma we are likelier to find metastases.

DR. SOWLES: I might add that this man is reasonably sick. Postoperatively he had a certain amount of intra-abdominal infection and is probably going to develop a pelvic abscess, if he survives to that stage; of course, the prognosis is bad.

DR. CASTLEMAN: The prognosis of lymphoma of the gastrointestinal tract is fairly good if the tumor is completely removed surgically. It is only when the lymphoma has involved the lymph nodes that the outlook is bad.

DR. SOWLES: I doubt very much that we completely removed the tumor, although we did excise a goodly portion.

CASE 30192

PRESENTATION OF CASE

A fifty-four-year-old Italian waiter was admitted to the hospital complaining of epigastric pain.

The patient was apparently well until three months before admission, at which time he noted mild pain in the epigastrium, squeezing in character and coming on especially at night. It was inter-

mittent, lasting for a day or two and then disappearing for a week at a time. It was aggravated by meat and fried foods, and later by all solid foods; it was unaffected by the ingestion of milk or soda and somewhat relieved by bowel movements. About two weeks before entry into the hospital, the pain became much severer and almost continuous. It was associated with several bouts of chilly feelings and profuse sweating, occurring at night. On several occasions he was unable to retain fluid, which, after having apparently become caught at the level of the xiphoid process, was promptly regurgitated. There was no associated nausea. His bowel movements had been regular until he became constipated a few days before admission. He had lost 20 pounds of weight over a period of two months. He drank one pint of whisky a day until about five years previously.

Physical examination revealed a man complaining of abdominal pain but in no acute distress. The skin was soft, moist and warm. The tongue was heavily coated, and the breath foul. The lungs were clear. The heart sounds were distant. There was tenderness to deep pressure in the epigastrium, but no masses were palpable.

The blood pressure was 130 systolic, 90 diastolic. The temperature was 101°F., the pulse 108, and the respirations 20.

Examination of the blood revealed a red-cell count of 5,500,000, with 16 gm. of hemoglobin, and a white-cell count varying from 11,000 to 17,000, with 70 to 80 per cent neutrophils that showed a moderate shift to the left. The urine was negative. The stools were light brown and hard; they gave a +++ guaiac test on admission but subsequently became negative. The blood protein and nonprotein nitrogen were within normal limits. The blood chloride was 98 milliequiv. per liter. Two bromsulfalein tests, at different times, showed 30 per cent and 15 per cent retention of dye after thirty minutes. A blood Hinton test was negative, as were a blood culture and tests for agglutinins against typhoid bacilli, Brucella and *Pasteurella tularensis*.

A gastrointestinal series revealed a 5-cm. area of esophageal narrowing above the cardia; the esophagus above this point was considerably dilated (Fig. 1). This area did not widen after the administration of amyl nitrite. Only a small amount of barium entered the stomach, and no defect could be demonstrated in the fundus. A barium enema revealed redundancy of the sigmoid. An esophagoscopy performed on the fifteenth hospital day revealed an area of reddening 4 cm. above the cardia. A biopsy of this area revealed acute and chronic inflammation, with epithelial hyperplasia and keratosis. Bougies (No. 12 to No. 24) were passed readily through the cardia, and subsequent x-ray examination revealed no residue in the esophagus, the barium passing readily into the stomach.

During his hospital stay the patient continued to complain of gnawing epigastric pain, which became severe on occasions. The temperature gradually rose to 103°F. At that time he appeared toxic, lethargic and somewhat incoherent. The pharynx was beefy red, and two throat cultures revealed a few colonies of beta-hemolytic streptococci. Both leaves of the diaphragm were elevated. A pleural

FIGURE 1. *Roentgenogram Showing Esophageal Dilatation.*

friction rub was heard over the right third rib anteriorly. A few sticky rales were audible at the right base, later replaced by numerous inspiratory and expiratory rales, associated with dullness and increased tactile and vocal fremitus. A roentgenogram of the chest revealed areas of density in the right lower and left upper lobes (Fig. 2). Because of the chest findings, sulfadiazine was administered in adequate dosage for an eight-day period, without apparent effect. The abdomen became increasingly distended, and the patient developed diarrhea alternating with periods of relative constipation.

Periods of elevation in temperature to 101 or 103°F. alternated with periods of almost normal

temperature. The chest condition showed improvement by physical and x-ray examination, but the patient remained lethargic and at times semistuporous, with only vague orientation regarding time and place. Neurologic examination revealed small irregular pupils that reacted sluggishly to light. The fundi were normal. Muscular coordination was poor. The abdominal and cremasteric reflexes were absent, and the deep tendon reflexes depressed. Vibration sense was diminished in the lower extremities. On lumbar puncture the spinal fluid was clear, under normal pressure and free of cells; the total protein was 73 mg. per 100 cc.

On the thirty-eighth hospital day the patient had an attack of sudden severe pain that caused him to sit up and writhe about the bed, clutching his epigastrium. He was pale and sweating, his lips and nails blue, his pulse feeble, and his blood pressure 60 systolic. The abdomen, however, remained soft. Within a few hours he returned to his usual state of lethargy. Four days later the stool was found to be tarry, and the guaiac test was ++++. On the following day, his forty-third in the hospital, he suffered another severe attack of abdominal pain, also associated with shock. The pain was relieved by morphine and atropine, but the patient expired forty minutes later.

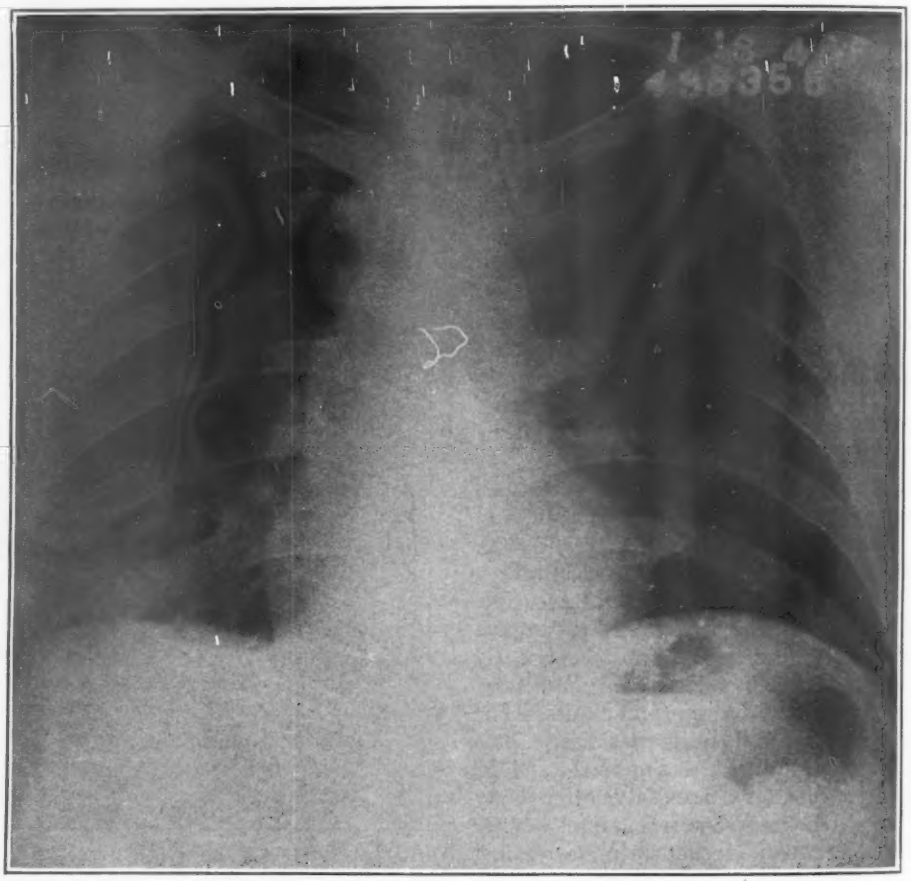

FIGURE 2. *Roentgenogram of the Chest Showing Areas of Density in the Right Lower Lung.*

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM B. BREED: I am sorry that I have so little time, because I had planned a nice wordy discussion of this case to cover up various spots of ignorance, and as you all know, the length of the discussion is inversely proportional to the accuracy. But now I am forced to gird my loins and be more accurate than I had planned.

When one is given a case that involves so many different structures in the body, such as the esophagus, the lungs, some viscus presumably under the diaphragm and possibly the central nervous system, it is important to try to hit on one pathologic process that will account for all of them. Of course the granulomas, such as syphilis and tuberculosis, stand first on such a list. The patient had negative blood Wassermann and Hinton tests, and also a spinal fluid that appears to have been negative. I am going to get, I hope, some information from Dr. Robbins. Perhaps he will help clarify the chest

situation, which is quite hopeless to my mind. In trying to explain these widespread lesions, the well-known standby of lymphoma comes into prominence.

I shall talk to Dr. Robbins about the x-ray films, or perhaps I shall just listen.

DR. LAURENCE L. ROBBINS: This is the chest film showing areas of increased density scattered throughout the right lower lung field, with a few in the left lung. I do not know the answer in this case, but I think that the patient had some reason to have changes in the chest because of the obstruction in the esophagus.

DR. BREED: This report is a little contradictory, since it says, "A roentgenogram of the chest revealed areas of density in the right lower and left upper lobes."

DR. ROBBINS: I did not put up the lateral film, in which there are a few areas of increased density in the left upper lobe.

The esophagus is dilated, as one can see from this film. Without any question the process was of considerable standing because, in addition to the size, there were fluid and food in the esophagus. This other film was taken later, after the bougienage, when there was no delay at the cardia. When I examined him the lower esophagus seemed to be funnel-shaped and looked like cardiospasm to a certain extent. The esophagus did not change with amyl nitrite, and at no time could I be sure of a defect in the stomach, although I did raise the question on the chest film whether there might have been something wrong with the fundus.

DR. BREED: That does not look like a metastatic process in the lung?

DR. ROBBINS: It is not characteristic of it.

DR. BREED: I am a bit disturbed because the record says that there was esophageal narrowing 5 cm. above the cardia.

DR. ROBBINS: It is not particularly clear in these films, but if this is the cardia there is an area of narrowing about 5 cm. above it.

DR. BREED: Did you call it cardiospasm?

DR. ROBBINS: I raised that question and the other alternative that one always worries about in that area.

DR. BREED: Dr. Edward B. Benedict apparently esophagoscoped this man, found a red mucosa and did a biopsy, which showed acute and chronic inflammation with epithelial hyperplasia and keratosis. What does that mean to you, Dr. Castleman?

DR. BENJAMIN CASTLEMAN: Only that there was some keratosis, which could have been the result of chronic inflammation.

DR. BREED: I think it is extremely unlikely that one diagnosis can explain the findings in the esophagus and the presumable lesion underneath the diaphragm, and I doubt that the correct diagnosis will be even mentioned before Dr. Castleman tells us about it.

Certainly the patient had a reasonably rapid and progressive toxic or septic process, with fever and epigastric pain, but with no obvious peritoneal irritation. On examination during all this time, his abdomen was said to have been soft. There was deep tenderness, which is not to my mind particularly significant. Looking at these x-ray films now, I think that this process could perfectly well have been a reflection of some sort of disease under the diaphragm.

Let us assume that the patient had cardiospasm or some other benign constriction of the esophagus above the cardia that was dilatable with bougies. I am going to assume that without going into detail, and I also believe that his main difficulty was under the diaphragm in the region of the liver. He had had a certain amount of alcohol for thirty years, and he exhibited some evidence of liver dysfunction. Possibly he had a hepatoma in a cirrhotic liver. Let us see if that adds up to anything. That would explain a good many of the symptoms. It would also explain, I believe, the lesions above the right diaphragm. It would not account for his sudden death, which I am unable to explain. The story gives one the impression of a ruptured viscus, but without any evidence of peritoneal irritation on examination, this seems to be an unlikely explanation. A subdiaphragmatic abscess or abscess in the liver, amebic or otherwise, might explain the picture. I believe that the neurologic findings were probably terminal and that he did not have actual disease of the nervous system. Certainly nothing of that nature is demonstrable in the record, and the findings on physical examination could have been preterminal.

In trying to arrive at a diagnosis it is a great mistake to guess too much. I am prepared, however, neither to make a diagnosis nor to guess the diagnosis. I merely say that I think the primary lesion was probably in or about the liver and that it probably was some sort of malignant process, not primarily one of infection: a hepatoma in a mildly cirrhotic liver is all right, but it is pure guesswork. One could name three or four different mortal diseases of a malignant nature, but I am not prepared to guess.

Do you want me to be more specific?

DR. CASTLEMAN: Yes.

DR. BREED: Do you want me to make one diagnosis?

DR. CASTLEMAN: That would be preferable.

DR. BREED: It would be pure guess, and I am not sure it is legitimate. Did he have one or two diseases? Is that a fair question?

DR. CASTLEMAN: Not exactly; but I am willing to say that he had two diseases that were related.

DR. BREED: Since I am pushed into a corner and have to guess, I shall say that he had a hepatoma secondary to a cirrhotic liver.

DR. EARLE M. CHAPMAN: I secretly enjoyed Dr. Breed's sweating. He was in exactly the same posi-

tion that I was in. I was completely puzzled and could not make a diagnosis. Dr. Paul D. White, who was previously on service, thought of a number of possibilities; and he, too, was wrong. Dr. Gerardo M. Balboni, who had been taking care of the patient for a long time, was convinced that he had Korsakoff's disease, with cirrhosis of the liver. We did not have much else to go on. Dr. Breed was astute in placing the disease below the diaphragm because Dr. Balboni and I put it above.

DR. BREED: But he died, do not forget that.

DR. CHAPMAN: He was going down hill so fast that we asked the Surgical Service to see him; they declared that he did not have a surgical abdomen.

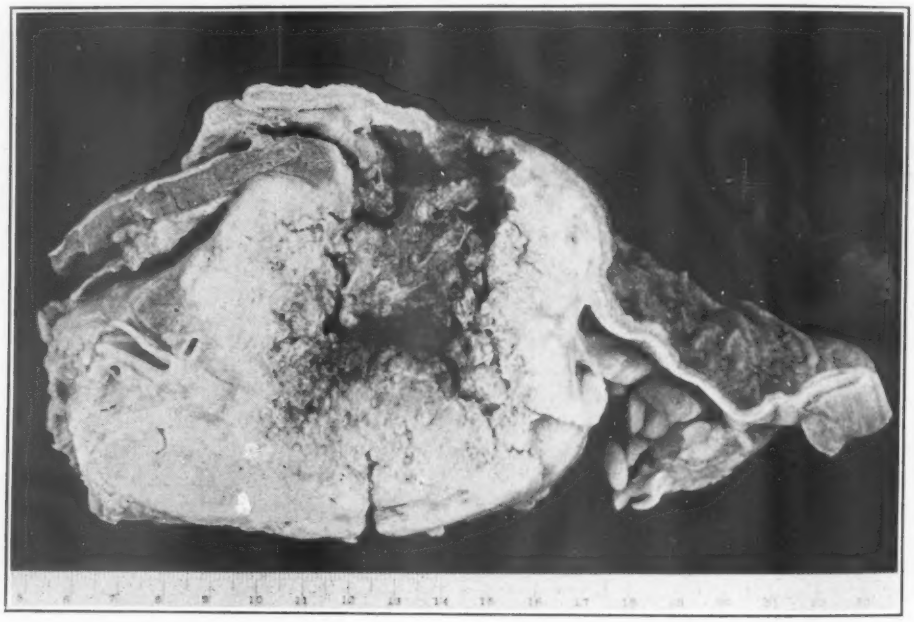

FIGURE 3.

At the first attack that is described he had pain. Dr. Madelaine Brown examined him neurologically, and during this examination he had a convulsive-like seizure, which was extremely dramatic. Five minutes later he was in shock, holding his abdomen and writhing in pain. We did not know what was wrong with him. He survived that attack, but died in a subsequent attack five days later.

DR. CASTLEMAN: Dr. Jones, have you any suggestions to offer?

DR. CHESTER M. JONES: I am sure that I cannot make a diagnosis, but from the facts given us there are certain things one has a right to mention.

In the first place one sees, although infrequently, acute abdominal pain with cirrhosis of the liver — so acute that the question of surgical intervention arises and severe enough to require morphine, a drug that can precipitate a fatal outcome. It is perfectly fair to suspect that this man may have had cirrhosis of the liver. That would account for a great many of the symptoms. It could also explain the agonizing abdominal pain with death within a few hours.

DR. BREED: You would not be willing to accept cirrhosis alone in this picture?

DR. JONES: So far as the pain and fever are concerned, yes; but I do not believe that cirrhosis was the whole or the true story.

The difficulty in swallowing is the other curious part of the story. One thing might be mentioned in defense of Dr. Benedict, who did the biopsy. It is frequently impossible to obtain an adequate specimen by esophagoscopy, owing to the presence of an area of inflammation just above the actual site of trouble, which may be carcinoma. Dr. Robbins also had to hedge on the x-ray interpretation of cardiospasm. The diagnosis of carcinoma ought to be seriously considered, and I gather that Dr. Robbins did consider it as a possibility.

Two other points are worthy of mention: the patient had evidence of a hepatic disorder and he was an Italian who had used a reasonable amount of alcohol. Cirrhosis is not an uncommon finding in this particular group. In addition, there was some dye retention, which bears out that possibility.

The bleeding is also interesting and has not been explained. It is quite possible that the patient had a carcinomatous lesion from which he was bleeding, or he might even have had varicosities just below the cardia, rather than above, as a cause of bleeding.

The story of mental confusion and the neurologic findings, — the absent reflexes and the diminished vibration sense, — the very red, sore mouth — which was certainly not due to a streptococcal infection — and the clear spinal fluid with definite ele-

vation in protein, all could go with deficiency disease. This would fit in with a Korsakoff's syndrome.

I think Dr. Breed is absolutely correct in refusing to be drawn into a flat diagnosis. He has shown good judgment. But I believe that cirrhosis was in the background and that there might have been a malignant process in addition, superimposed or adjacent to it.

Clinical Diagnoses

Alcoholic cirrhosis of liver?

Korsakoff's psychosis.

Carcinoma of stomach?

Dr. Breed's Diagnosis

Cirrhosis of liver, with superimposed hepatoma.

Anatomical Diagnoses

Epidermoid carcinoma (Grade III), of esophagus, with metastases to mediastinal and retroperitoneal lymph nodes, pancreas and esophagus.

Perforation of pancreatic metastasis into cardiac end of stomach.

Massive hemorrhage into stomach.

Lipid pneumonia.

Multiple foci of degeneration in cerebral cortex.

Pathological Discussion

Dr. Castleman: The autopsy on this man showed a large mass in the abdomen that apparently invaded, or was part of, the body and tail of the pancreas; this mass had perforated into the stomach (Fig. 3). At the time of the autopsy we thought that that was the whole story. The stomach was filled with a huge cast of clotted blood.

Later, however, in the esophagus, 5 or 6 cm. above the cardia, we found an ulcerated lesion measuring 3 by 2 cm. that had infiltrated the wall; about 2 cm. above that was a similar but smaller lesion, and there was a third one above that. These three esophageal lesions, as well as the mass in the abdomen, proved to be epidermoid carcinoma. The tumor was therefore primary in the esophagus and not in the pancreas, and the "pancreatic mass" proved to be a large group of cancerous retroperitoneal lymph nodes that had invaded and replaced the body and tail of the pancreas.

That does not explain the lesions in the lung, which, grossly, were moderately firm and believed to be carcinomatous metastases. These proved to be areas of oil-aspiration pneumonia or lipid pneumonia, which is often found in patients with cardiospasm or other lesions in the esophagus. The man had probably been taking a lot of mineral oil, and during the course of time appreciable amounts of oil had gained access to the lungs.

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NEW MEDICAL FOOD REGULATIONS

A point system of food rationing has now been in operation for well over a year, having been inaugurated on March 1, 1943. The fact that our nation continues to eat, and to eat moderately well in addition to supplying foods to other countries, seems to indicate that the system works in a reasonably satisfactory manner. It has its faults and its inadequacies; abuses have crept in and black markets have flourished, human nature being what it is, yet we have kept ourselves not only free from want, but well nourished.

On account of the obvious need for special dietary consideration on the part of certain institutions and population groups, the director of the War Food Administration requested the National Research Council in April, 1943, to appoint a committee of physicians to advise concerning the extent of these special needs and the best method of meeting them. The Subcommittee on Medical Food Requirements, within the Division of Medical Science of the National Research Council, under the chairmanship of Dr. William D. Stroud, of Philadelphia, resulted, and its recommendations were published in the October 16 and 23, 1943, issues of the *Journal of the American Medical Association*.

As of April 6, 1944, thirteen months and six days after the inauguration of point rationing, the Office of Price Administration adopted the recommendations of the subcommittee, practically without change! For over a year each local board, each state and each region have solved their own food-rationing problems as they apply to the care of the sick, and in many instances have devised their own more or less complex, more or less satisfactory systems of operation. The mills of the gods certainly grind exceeding slow, whatever the quality of their meal.

In June, 1943, at the request of the District Rationing Officer, the president of the Massachusetts Medical Society appointed an advisory committee to aid in the medical aspects of food rationing. The Boston district, which originally extended westward to Worcester, was enlarged in October to include the entire state, and during the winter was merged with the New England Regional Office, by some sort of phagocytic process. There has been a tendency, consequently, to enlarge the usefulness of the Massachusetts committee, since Rhode Island is so far the only other New England state with a medical advisory committee.

The new regulations, adopted at long last by the Office of Price Administration, are more drastic than the homespun principles under which the district has functioned for nearly a year. The list of diseases that automatically rate extra rations is a short one, consisting only of diabetes mellitus, active tuberculosis, chronic nephritis of the nephrotic type, cirrhosis of the liver, severe hepatitis, chronic suppurative diseases, severe burns, gastrointestinal lesions and pregnancy for extra meats, fats and oils, and diabetes and active tuberculosis for extra allot-

ments of processed foods. All other requests must be approved by the New England Regional Office — an extra hazard for those physicians who still ask additional allotments for their patients with gallbladder disease, heart conditions of all types, obesity, anemia, pneumonia and polyneuritis.

Furthermore, with the recent lowering of point values and the virtual abandonment of rationing for many foods, it seems likely that little will be needed for anyone in the nature of extra concessions.

FREDERICK II OF HOHENSTAUFEN AND HIS FAVORITE SPORT

A CULTURED, gifted, thirteenth-century pioneer in medical education and economics, a fighting king, the founder of the University of Naples in 1224 (the first school in Europe to be established by a charter), a student of mathematics, natural history and philosophy, a man with an absorbing passion for the now nearly extinct sport of falconry and the writer of a book on the subject, composed in the critical spirit of modern science — such was Frederick II of Hohenstaufen, Holy Roman Emperor, King of Sicily and Jerusalem.

His treatise on falconry is one of the most important zoological works of the Middle Ages. The original text, compiled by himself, was lost in a battle before Parma, but a devoted son, Manfred, prepared a revision of the first two books, the basis for the printed editions that followed. Fortunately at least six other contemporary manuscripts of the complete work are known, and six more of the two-book manuscript. There have been four printed editions of the first two books, but none of the entire work until the one recently issued by the late American ophthalmologist, Dr. Casey A. Wood, and his secretary, F. Marjorie Fyfe.[1] After his retirement from practice in Chicago, Wood spent years in Europe probing into and comparing the texts of every manuscript of this book that he could find.[2] In the University Library at Bologna he discovered the fullest text, and in the Vatican Library at Rome the one most superbly illustrated. Wood's translation covers over four hundred large pages, an indication of how detailed was the study of Frederick II. The king recorded for the first time such observations as the pneumaticity of the bones, the form of the sternum, the mechanical condition of flight, and migrations. Frederick experimented on the artificial incubation of eggs. The scientific world owes much to Wood for his clear rendering of the Latin manuscripts. By publishing the whole work, much new material has been added, particularly on the use of the lure, on the training of falcons in a cast, on crane hawking with gyrfalcons, on heron hawking with sakers and on hawking at the brook with the peregrine falcon.

To Wood's translation of *De Arte Venandi cum Avibus*, Walter Schlüter has added a chapter on falconry in modern times. Falconry was a favorite sport of all classes in Europe up to the time of the French Revolution. It has survived in a few areas. In England there are examples of family falconers running through many generations, such as the Fleming family of Barochan Tower, who, up to recent years, were still flying falcons in England and in India. Holland, France, Germany, Australia and America all have small but active centers of falconry, but the great days, when Frederick II had hunting lodges scattered throughout the mountains of Sicily and southern Italy, in places all too familiar today in our daily news, are long past.

Frederick has other claims to fame besides his scientific book on falconry. He gave to Sicily a remarkable code of laws, promulgating a regulation of the practice of medicine, the first elaborate work of its kind. To Salerno, the great medical school of his day, he granted the exclusive right to confer the license to practice medicine in the whole kingdom, and his stipulation for the length of medical studies has a modern ring: five years, plus one year of practical work under the guidance of an experienced physician, corresponding to one year of internship. A second postgraduate year was taken by surgeons, similar to a residency. Are we less wise than Frederick II in curtailing medical education in wartime, whereas, he, who lived in a continuous state of war, provided five or six years for medical training? Possibly the twentieth century has something to learn from the thirteenth.

REFERENCES

1. *The Art of Falconry being the De Arte Venandi cum Avibus of Frederick II of Hohenstaufen.* Translated and edited by Casey A. Wood and F. Marjorie Fyfe. 637 pp. Stanford University, California: Stanford University Press, 1943.
2. Editorial. Casey Wood (1856–1942) and American medicine. *New Eng. J. Med.* 226:1051, 1942.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

PARLOW — George G. Parlow, M.D., of Wareham, died April 20. He was in his seventy-fifth year.

Dr. Parlow received his degree from the College of Physicians and Surgeons, Boston, in 1905. He was a member of the Massachusetts Medical Society and the American Medical Association.

CORRESPONDENCE

AN EXPRESSION OF APPRECIATION

To the Editor: National Hospital Day is Friday, May 12. This year in bringing hospitals to the attention of the public, emphasis is being placed on what the hospitals are doing in keeping our civilian population well and at work during the third year of the war. We believe that we are making a vital contribution to the war effort, and that the public should be informed regarding some of the difficulties being encountered in the operation of our institutions.

The committee arranging for the observance of National Hospital Day in Massachusetts was unanimous in requesting that I express to the members of the Massachusetts Medical Society, through the *New England Journal of Medicine*, our very real appreciation of the contribution the doctors on our hospital staffs are making in keeping our hospitals operating. Many who had retired from active practice have come back to work long hours. The rest of the doctors have greatly increased their burdens in order to give adequate care to our communities. As president of the Massachusetts Hospital Association, in the name of the administrators of our hospitals, I wish to thank the members of the Massachusetts Medical Society for the invaluable contribution they are making to the continued operation of our institutions. Without their devoted service, it would be impossible to keep our doors open to the public.

GEORGE A. MACIVER, *President*
Massachusetts Hospital Association

BOARD OF REGISTRATION IN MEDICINE

To the Editor: Recently a member of the medical profession of Massachusetts was quoted by the newspapers as saying, in regard to certain matters concerning the Board of Registration in Medicine, that the Board had been "a sort of plague spot for years." The statement did not say what sort of plague spot nor how long it had been a plague spot, but the quotation went on to state that the conditions, however, had been improving. This also was not made clear and in view of the fact that the Governor had seen fit to "oust" three members of the Board, according to newspaper reports, one wonders in what the "improvement" had consisted. The situation has been left in a very unsatisfactory state. The Governor is reported to have said "the less said about it the better." The Attorney-General is reported to have said that he found no ground for criminal action. This may be taken to mean that there was no violation of the letter of the law.

I am writing because I think the medical profession and the public have a right to know more about the background of the situation and because I know nothing about the specific facts in the late incident, although I am familiar through years of experience with the work of the Board. Therefore, I write impersonally and I shall attempt to point out the framework of reference within which the discussion should take place.

The duties of the Board lie, in general, in two fields—the licensing and the unlicensing of physicians. The former is usually done after examination, although occasionally, in the case of a physician whose license had been revoked by the Board, without examination, but a license is revoked only after a hearing, as provided by law.

What qualifications does the law set for performing the first duty, which includes the setting of an examination that shall be practical in character and sufficiently thorough to test the qualification of the candidate for the practice of medicine? Substantially these: the candidate for appointment shall himself be licensed by the Board and shall be engaged in the practice of medicine for ten years, but he shall *not* be connected with a medical school. This last phrase excludes from the Board the physicians who are likely to know how to set an examination and the examinations are, therefore, more likely to be an unsatisfactory test than if they were given by someone familiar with teaching. Is it going too far to say that the law sets a premium on not knowing how to set an examination?

What of the ten years of practice? Of what value is that? Probably it impairs the competence to set an examination, for the farther the candidate is from his own student days the less likely he is to be familiar with the technic of that procedure. But it is in the unlicensing of physicians that the ten years of experience in practice may be invaluable. The board member has had an opportunity to experience the problems met in actual practice and is in a better position to exercise discretion in deciding whether a physician has been guilty of "gross misconduct in the practice of his profession."

It would be interesting to go into the history of that disqualification — connection with a medical school — and find out why it was introduced into the law and why it has not been deleted when in the opinion of many persons it has no present usefulness and may actually prove to be an obstacle to attaining one of the purposes for which the Board exists. Thus the first difficulty is with the law.

The second difficulty is of a different character: not all governors take the Board seriously. Again and again physicians have been appointed to positions of trust, when consulting the records of the Board might have indicated the impropriety of the appointment. It is not a question of asking the Board or its chairman or its secretary for recommendation or disapproval. It is asking for the record, the facts. Has the candidate ever been reported to the Board for any alleged impropriety in practice, what was the nature of the complaint, and what were the findings of the Board?

Appointment to the Board carries an inconsiderable salary but for some physicians prestige is enhanced. Too often the appointment is in payment for some political debt or as a reward for medical services to the community (or to the executive) faithfully performed. The law says that the candidate shall have been engaged in practice for ten years, not for one hundred and ten years, and the candidate should be young enough to have vigor to carry through carefully and conscientiously what some persons may regard as the chore of evaluating and grading justly six, seven or eight hundred examination books each year. Although the work done at ten Board meetings a year may be of great importance, it is an incomparably lighter burden than properly grading the examination books. Rarely does the question seem to be asked, Has the candidate fitness for setting examinations, understanding, firmness, wisdom, integrity, a judicial mind?

At one time there were on the Board of Registration in Medicine in Massachusetts, two members who had had cerebral hemorrhage. The presumption was against these men being able to act with proper discrimination if subjected to stress, or in cases involving delicate weighing of evidence. This brings us to the third difficulty.

Under the statute, the Board may under certain circumstances exercise its discretion, which means that individual members must exercise their discretion. If the executive has appointed indiscreet persons, the system breaks down under pressure. In the nature of things stress is inevitable. By no possible effort can the procedure be made mechanical. On the one hand there are the welfare, happiness, and lives of the citizens of the Commonwealth, all human beings; on the other hand are candidates for licensure, eager for practice, with various degrees of qualification, also human beings. Judgment concerning qualification for practice requires a fine discrimination, a scalpel wielded with intelligent skill, not a blunderbuss fired in all directions.

The problems presented by the Board of Registration in Medicine are in part problems for the medical profession. The question that I should like to bring home to every physician in Massachusetts who is really interested in upholding the high ideals of the profession by trying to realize them is, What have *you* done to change conditions in this state so that no one can say with justice that we have in Massachusetts a plague spot?

STEPHEN RUSHMORE, M.D.

520 Commonwealth Avenue
Boston

(*Notices on page xii*)

Little Chief Redskin gets Big Itch!

FORAYS into the forests and fields by our own little followers of the Redskin bring them many unhappy meetings with the enemies, *RHUS toxicodendron* (poison ivy) and *RHUS diversiloba* (poison oak).

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1. Kerr, W. H. et al.: Nebr. State Med. J., 26:129, 1941.

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NOTICES

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, May 16, at 12 noon. Dr. Dwight O'Hara will speak on the subject "Mechanisms Concerned with the Inception of Pneumonia." Dr. Cornelius N. Garland will preside.

Physicians are cordially invited to attend.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The annual meeting of the Massachusetts Society of Examining Physicians will be held on Wednesday evening, May 17, at the Copley Plaza Hotel, Boston.

Dinner is scheduled for 6:30 p.m., to be followed by a business meeting, with election of officers and new members. Dr. Harrison L. McLaughlin, professor of surgery at Columbia University and assistant chief-of-staff of the Orthopedic Service at the Presbyterian Hospital, New York City, will present a paper, "Muscular and Tendinous Defects of the Shoulder and Their Repair," with motion pictures and Kodachrome slides. Dr. Joseph H. Shortell will discuss the paper.

Reservations for the dinner ($3.50 per person) may be made by writing to Miss Anne Rodman, Assistant Secretary, 157 Fourth Street, Medford, Massachusetts.

NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held on Friday, May 26, at 8:15 p.m., at the Boston Medical Library. A short annual business meeting will precede the program.

PROGRAM

Cardiovascular Dynamics in Fever and Shock following Injections of Bacterial Toxins. Drs. A. Stone Freedberg and H. Haimovici-Lenobel.

The Early Results of the Treatment of One Hundred and Fifty-Six Hypertensive Patients by Radical (Lumbodorsal) Splanchnicectomy. Dr. Reginald H. Smithwick.

Coronary Artery Disease among Physicians, and Other Correlations. Drs. Joseph A. Hindle and Samuel A. Levine.

A Preliminary Report of the Effects of Antuitrin-S on the Rheumatic State. Dr. Timothy F. Brewer.

On Some Antagonistic Effects of Digitalis Glucosides to Vagus Stimulation. Drs. Aldo A. Luisada and H. Mautner.

Interested physicians and medical students are cordially invited to attend.

(*Continued on page xv*)

NOTICES (*Continued from page xii*)

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning

Thursday, May 18

Thursday, May 18

*9:00-10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

Friday, May 19

*9:00-10:00 a.m. Diagnosis of Pancreatic Disease. Dr. Joseph H. Pratt. Joseph H. Pratt Diagnostic Hospital.

Saturday, May 20

*9:00-10:00 a.m. Medical clinic. Dr. William Dameshek. Joseph H. Pratt Diagnostic Hospital.

*10:00-11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

Monday, May 22

*9:00-10:00 a.m. Medical clinic. Dr. Samuel Proger. Joseph H. Pratt Diagnostic Hospital.

*12:15-1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

5:00-7:00 p.m. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

Tuesday, May 23

Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

*9:00-10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

Wednesday, May 24

Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

*9:00-10:00 a.m. Prefrontal Lobectomy Indications and Results. Dr. Kurt Goldstein. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

May 11. Problems of the Department of Industrial Accidents. Mrs. Emma S. Tousant. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

May 16. South End Medical Club. Page xii.

May 17. Massachusetts Society of Examining Physicians. Page xii.

May 26. New England Heart Association. Page xii.

June 7-13. American Board of Obstetrics and Gynecology. Page x, issue of March 23.

June 8-10. American Board of Internal Medicine. Page x, issue of April 20.

June 12-16. American Medical Association. Page 798, issue of November 18.

June 12-16. American Physicians' Art Association. Page x, issue of March 2.

October 3-5. American Public Health Association. Page ix, issue of March 30.

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NUTRITIONAL ANEMIA IN INFANTS

REASONS FOR EARLY FEEDING OF PABLUM (OR PABENA)

1. The infant's initial store of iron is rapidly depleted during the first months of life. (Mackay,[1] Elvehjem[2]). About 30% of the iron freed from the hemoglobin during the first two months is lost, and while hemoglobin destruction takes place, all infants are in negative iron balance. (Jeans,[3] and Usher, et al.[4]).

2. During the early months of life the infant obtains very little iron from milk — 1.44 mg. per day from the average bottle formula of 20 ounces or possibly 1.7 mg. per day from 28 ounces of breast milk. (Holt,[5] Jeans[3]). The incidence of nutritional anemia has been found to be high among infants confined largely to a diet of cow's milk. (Davidson, et al.[6] Usher, et al.,[4] Mackay[1]).

For these reasons and also because of the low hemoglobin values so frequent among pregnant and nursing mothers (Strauss,[7] and Gottlieb and Strean[8]), the pediatric trend is constantly toward the addition of iron-containing foods at an early age, both to normal infants and those with pylorospasm. (Neff,[9] Blatt,[10] Brennemann,[11] Monypenny[12]).

THE CHOICE OF THE IRON-CONTAINING FOOD

1. Many foods high in iron actually add very little to the diet because much of the mineral is lost in cooking or because the amount fed is necessarily small or because the food has a high percentage of water. Strained spinach, for instance, contains only 1 to 1.4 mg. of iron per 100 Gm. (Bridges[13]).

2. To be effective, food iron should be soluble. Some foods fairly high in total iron are low in soluble iron. Thus egg yolk and liver have less soluble iron than does farina, which is very low in total iron. (Summerfeldt[14]). Oxalate-containing leafy vegetables are low in soluble iron and appear not to be well utilized as a source of iron by infants. (Kohler, et al.,[15] and Stearns[16]).

3. **Pablum (and Pabena) are high both in total iron (30 mg. per 100 Gm.) and soluble iron (7.8 mg. per 100 Gm.) and can be fed in significant amounts at an early age, without digestive upsets. (Blatt,[10] Monypenny[12]). Clinical studies of sick and well babies have shown Pablum to be of value in raising hemoglobin values (Crimm, et al.,[17] Summerfeldt and Ross[18]), even when egg yolk and spinach were not effective (Stearns[16]).**

Pablum, a palatable mixed cereal food, vitamin and mineral enriched, and cooked thoroughly and dried, consists of wheatmeal (farina), oatmeal, wheat embryo, cornmeal, powdered beef bone, sodium chloride, alfalfa leaf, brewers' yeast, and reduced iron. (The oatmeal form of Pablum is called Pabena.)

[1-18] **Bibliography on request.**

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